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ACUTE ISCHEMIC NECROSIS OF THE KIDNEY

A CLINICOPATHOLOGIC AND EXPERIMENTAL STUDY

ABRAHAM PENNER, M.D.
AND
ALICE IDA BERNHEIM, M.D.
NEW YORK

In an attempt to reproduce experimentally the acute necrotizing enteritis which we believe to be due to the compensatory mechanisms called into play in shock, we were led to use epinephrine intraperitoneally.[1] In this manner we were able to cause lesions which resembled those described in man.[2] However, in addition to the lesions observed in the gastrointestinal tracts of our animals we noted renal changes which grossly resembled those seen in acute bilateral cortical necrosis of the kidney.

We therefore reviewed the clinical and pathologic material at our disposal in order to see if similar renal lesions occurred in shock. It is the purpose of this communication to present the human and experimental material relevant to this problem.

HISTORICAL REVIEW

Bilateral cortical necrosis of the kidneys was first described by Juhel-Rénoy,[3] in 1885, in a 16 year old girl who died in the course of an attack of scarlet fever. Since that time the renal condition has been reported in association with a variety of primary conditions. In the vast majority of the cases it has been observed in the course of pregnancy,[4] but it has also been noted in association with diphtheria,[5] cholera,[6] "influenza," [6] dysentery,[7] burns [8] and trauma,[9] as well as following

From the Laboratories of the Mount Sinai Hospital.

1. Penner, A., and Bernheim, A. I.: J. Exper. Med. **70**:453, 1939.
2. Penner, A., and Bernheim, A. I.: Arch. Path. (*a*) **27**:966, 1939; (*b*) **28**:129, 1939.
3. Juhel-Rénoy, E.: Arch. gén. de méd. **17**:385, 1886.
4. Gaspar, I. A.: Am. J. Clin. Path. **8**:281, 1938.
5. Stoeckenius, W.: Beitr. z. path. Anat. u. z. allg. Path. **69**:373, 1921.
6. Beneke, R., in Zülzer, W., and Oberländer, F. M.: Klinisches Handbuch der Harn- und Sexualorgane, Leipzig, F. C. W. Vogel, 1894, pt. 1, p. 148.
7. Fahr, T. H., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6, p. 143.

(Footnotes continued on next page)

operations.[9a, d] It is not our purpose to review all the pertinent casuistic material but to indicate what we believe to be the important and relevant data in those cases in which the clinical and pathologic material is sufficiently complete to permit analysis. For this reason we omit from detailed consideration the cases reported by Beneke,[6] who described necrosis of the kidneys in the algid state of cholera and in "influenza" (2 cases) which was so violent that death occurred rapidly. He compared the lesions with those seen in eclampsia.

In 1927 Neuberger[9a] described 3 cases in which renal infarction followed trauma or operation. There was a traumatic rupture of the liver in the first case; there was a rupture of the spleen with a hemoperitoneum following an attempt at suicide in the second, and in the third case there had been an operation for intestinal obstruction resulting from sigmoid volvulus. In the last instance the patient was in prolonged shock postoperatively and died two weeks later. Neuberger considered the lesions to be due to a traumatic angiospasm similar to the traumatic segmental arterial spasm which occurred in vessels of the leg as a result of war injuries.

In the same year Furtwaengler[9b] reported his now classic case of "diffuse cortical necrosis of both kidneys following liver rupture." This concerned a 22 year old woman who in an automobile accident in which her car was overturned had the steering wheel suddenly forced into the right upper quadrant of her abdomen. When seen, she was in "shock" and was pale, cold and somnolent. Her pulse rate ranged from 120 to 130 beats per minute and was barely palpable. Laparotomy revealed a tear in the right lobe of the liver with pulpification of the liver substance. There was no evidence of trauma to the kidneys. She was given a blood transfusion, and saline solution was injected intravenously. On the next day she was pulseless, cold and unconscious. She was given a transfusion of 1,200 cc. of blood. No urine was obtained by catheterization. On the second postoperative day 3 to 4 cc. of urine was obtained and was found to contain albumin, white blood cells, epithelial cells and hyaline, granular and cellular casts. She died three days after the operation. At autopsy bilateral renal cortical necrosis was found. Furtwaengler attributed the lesions to an angiospasm caused by the presence in the blood stream of toxins derived from the traumatized liver.

Since 1932 Helwig and his associates[9c,d] have been particularly interested in the occurrence of varying degrees of renal parenchymal damage as related to trauma of the liver. Their first case presented clinical features almost identical with those of Furtwaengler's. At postmortem examination they found renal changes of an inflammatory and degenerative nature with epithelial necrosis which "differs from Furtwaengler's only in degree." In their description of the intestine they mentioned swelling of the mucosa and submucosa in the region of the papilla of Vater, as well as submucous and subserous hemorrhages in the colon. These changes are similar to those which we have found to occur in shock of the most varied causation. Similar renal and intestinal findings were reported by Helwig and Schultz[9d] in a series of 6 cases reported in the same year. They ascribed the renal lesions to the action on the kidneys of some potent toxin produced in the liver by hemorrhagic necrosis.

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8. Polland, A.: Wien. klin. Wchnschr. **20**:223, 1907.

9. (*a*) Neuberger, K.: Virchows Arch. f. path. Anat. **265**:789, 1927. (*b*) Furtwaengler, A.: Krankheitsforschung **4**:349, 1927. (*c*) Helwig, F. C., and Orr, T. G.: Arch. Surg. **24**:136, 1932. (*d*) Helwig, F. C., and Schutz, C. B.:

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Similar cases have been described by Husfeldt and Bjering [9e] and are of great interest from the clinical standpoint. In their second case, which was followed very carefully, a 46 year old man sustained a pelvic fracture as a result of a crushing injury. It was found that the blood urea rose to 138 mg. per hundred cubic centimeters within forty-eight hours after the trauma and reached 333 mg. per hundred cubic centimeters on the eighth day. During the last four days of life the man was anuric, and his systolic blood pressure rose to 160-170 systolic. At autopsy the glomeruli were found to be devoid of blood. No thrombi were seen. The tubular epithelium was desquamated and showed necrosis. The authors considered that the renal insufficiency resembled the clinical state found in acute glomerulonephritis and that their patients died in uremia. They felt that the renal lesions were in some way related to the shock which was present but that the exact mechanism involved was obscure.

A very interesting instance of bilateral cortical necrosis of the kidney was reported by Gaspar.[4] The patient was a 33 year old pregnant multipara whose urine showed no abnormalities even in this final pregnancy prior to the present hospital admission. She was admitted to the hospital because of profuse vaginal bleeding. Pregnancy was terminated with the use of a Vorhees bag. Severe uterine bleeding necessitated a transfusion. Urine obtained at this time showed albumin (4 plus), no sugar, occasional leukocytes and many red blood cells and hyaline casts. Despite the forcing of fluids, anuria developed. Cerebral symptoms of uremia appeared, and decapsulation of the left kidney was therefore performed. Following this, although she became worse, small amounts of urine were obtained. Her temperature rose, and with this acidosis developed, with a carbon dioxide–combining power of 13 volumes per cent. She died thirteen days after admission. One day before death the nonprotein nitrogen was 138 mg. per hundred cubic centimeters. At autopsy typical bilateral cortical necrosis of the kidneys was found.

Similar cases have been described by Scriver [10] in which cortical necrosis followed postabortal hemorrhage. In 14 of his 33 cases the renal disease was associated with retroplacental hemorrhage. The susceptibility of pregnant women to shock has recently been emphasized by Lochrane.[11]

REPORT OF CASES

Case 1.—A 49 year old laborer was admitted to the surgical service of Dr. Ralph Colp with an irreducible strangulated right inguinal hernia. This had occurred twenty-seven hours before admission. There was evidence of complete intestinal obstruction with repeated vomiting and failure to pass feces or flatus.

On admission he was acutely ill and dehydrated. His tongue was dry; his blood pressure was 114 systolic and 88 diastolic, the urine showed a specific gravity of 1.040 but no albumin, sugar or acetone. There were occasional white blood cells and red blood cells in the sediment. There was a diffuse increase in resistance all over the abdomen, with definite rebound tenderness in both lower quadrants. Borborygmi were heard all over the abdomen. The right scrotum was filled with a tender, swollen, nontranslucent mass. Roentgen examination

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Surg., Gynec. & Obst. **55**:570, 1932. (*e*) Husfeldt, E., and Bjering, T.: Acta med. Scandinav. **91**:279, 1937.

10. Scriver, W. de M.; Berglund, H., and Medes, G.: The Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935, p. 417.

11. Lochrane, C. D.: Practitioner **143**:317, 1939.

of the abdomen revealed distended loops of small intestine in the left upper quadrant, which were considered indicative of partial intestinal obstruction.

Shortly after admission herniorrhaphy was performed, with reduction of the hernia and resection of a piece of omentum. There was a segment of ileum present in the sac. The temperature rose to 102 F. the second day after operation. The next day the urine revealed a specific gravity of 1.040 and albumin (1 plus) but no sugar or acetone. The sediment contained 3 to 4 white blood cells per high power field, occasional red blood cells, occasional hyaline and fatty and finely granular casts. Although there was a considerable drainage of sanguinous material through a Levine tube, obstructive symptoms again became suddenly intense. The abdomen was therefore explored a second time on the sixth day after admission, and it was found that the terminal part of the ileum was obstructed by a band of omentum which was adherent to the hernial ring. This was released, and an enterostomy was made just proximal to the site of obstruction.

The patient's condition prior to this operation was "poor." At the close of the operation he became cyanotic and the respirations shallow. He was given a 25 per cent solution of pyridine beta-carbonic acid diethylamide (coramine) and epinephrine hydrochloride intravenously and was placed in a Drinker respirator. However, his condition became worse, and he died in the operating room with "rapid failure of his pulse."

Autopsy was performed about twenty-three hours after death. The heart weighed 275 Gm., and except for mild arteriosclerotic changes and narrowing of the anterior descending branch of the left coronary artery, no significant changes were observed. There was bronchopneumonia in the lower lobe of the left lung and the middle and lower lobes of the right lung. There were severe bilateral pulmonary congestion and edema. No pulmonary infarcts were noted. There were interlobar pleural adhesions. The liver showed fatty changes. The pancreas showed lipomatosis. The spleen weighed 200 Gm. The pulp was slightly diffluent and contained a 5 mm. triangular area of yellowish gray tissue at the periphery of the cut surface. The vessels showed no unusual features. The adrenals were without gross change.

The kidneys weighed 225 Gm. each, They were large and firm. The capsules stripped with ease, revealing smooth tan-colored surfaces. In the upper pole of the right kidney and in the lower pole of the left kidney on the anterior surface were round, grayish white areas measuring 4 to 5 mm. in diameter. These were not depressed. The cut surface of each kidney was pale tan. The outer portion of the cortex of each organ in the region mentioned showed a triangular area with its base facing the capsule. These measured 4 mm. on edge and were grayish yellow. Immediately surrounding each of these areas was a narrow, deeply injected zone. Several similar small grayish areas were found elsewhere in the cortex. The corticomedullary demarcation was distinct. The pelvis and ureters presented no outstanding features. The renal arteries and veins showed no thrombi or emboli. Except for a small hydrocele of the right testicle, the rest of the genitourinary tract was without change.

The esophagus showed no changes except for the incidental finding of a firm intramural nodule, measuring 4.5 by 2.0 by 2.0 cm. The stomach presented an unusual appearance. The mucosa of the cardia and the proximal two thirds of the fundus was covered by a shaggy olive-green membrane. This was finely honeycombed and patchy. Between the membranous portions the mucosa was deeply injected. The distal third of the fundus and the pylorus were not unusual.

There was diffuse fibrinous peritonitis. The visceral peritoneum of both the large and the small bowel was dull and covered irregularly by thin white fibrinous material. There was no excess of peritoneal fluid. The ileostomy stoma was

located approximately 142 cm. from the ileocecal valve. Attached to the ileocecal junction was one end of the band of omentum which had been divided and ligated at the final operation. The other ligated end of the divided omental band was found attached to the right abdominal inguinal ring. A piece of fat, 4 cm. long and 1 cm. wide, was found sutured to the serosa of the ileum 120 cm. from the ileocecal junction. On either side of this the wall of the ileum was discolored green to greenish blue for a distance of several centimeters. When the intestines were opened, the mucosa of the duodenum presented no unusual features. Beginning at the duodenojejunal junction, for a distance of 45 cm., the jejunal mucosa was covered with a shaggy green necrotic membrane. The mucosa of the ileum in the region of the ileostomy was not unusual for a distance of 6 to 8 cm. on either side, but beyond this there were scattered areas of congestion.

Microscopic examination of the heart, liver, adrenals, prostate and bone marrow gave no pertinent information. The lungs presented histologic confirmation of the gross findings of bronchopneumonia, pulmonary emphysema and edema. The pancreas showed a small amount of fine interacinar fibrosis and squamous metaplasia of the duct epithelium in one area. The nodule in the esophagus was found to be a fibromyoma. Severe postmortem changes in the stomach prevented evaluation of the lesion. The small intestine also showed severe postmortem autolytic changes, but, in addition, the areas showing gross necrosis exhibited striking widening of the submucosal layer of the wall by severe submucosal congestion and edema, the latter predominating. Some of the submucosal vessels were distended with red blood cells, some with plasma and a few with homogeneous casts. There was, in addition, leukocytic infiltration, more prominent in several areas at the base of the mucosa. This was also present in small amounts diffusely throughout the submucosa and connective tissue stroma of the muscular and serosal layers.

The tissue of the spleen was fragmented, evidencing its soft consistence. Throughout, there was severe congestion. There was one fairly large area of acute necrosis, involving both the trabeculae and the splenic parenchyma. Here, the underlying structure was still discernible. Fibrin was concentrated at the periphery of this area, while the central portion also showed fibrin and nuclear debris intermingled with preserved red blood cells and partially preserved arteries, follicles and septums. There was no increase in leukocytes and no bacteria were seen.

While in the kidneys the obvious large infarcts were the major gross findings, the microscopic feature which was of greatest interest was the presence of isolated necrotic convoluted tubules at some distance from the major infarcts as well as in sections which showed no gross infarcts. Serial sections in these regions showed that the involved tubules were topographically related to individual glomeruli in which deviations from the normal of varying degree were observable. The most consistent of these was the presence of protein fluid in the capsular spaces. This was occasionally associated with red blood cells (fig. 1*A*). The glomerular tufts showed varying degrees of anemia. No emboli or thromboses were found in the afferent or efferent arterioles of these glomeruli. The walls of the capillary tufts in these glomeruli occasionally appeared somewhat thicker than usual. In the neighborhood of such glomeruli the intertubular stroma was edematous, the edema being especially noted around the larger arteries. Most of such involved tubules and glomeruli were seen to lie in the subcortical zone.

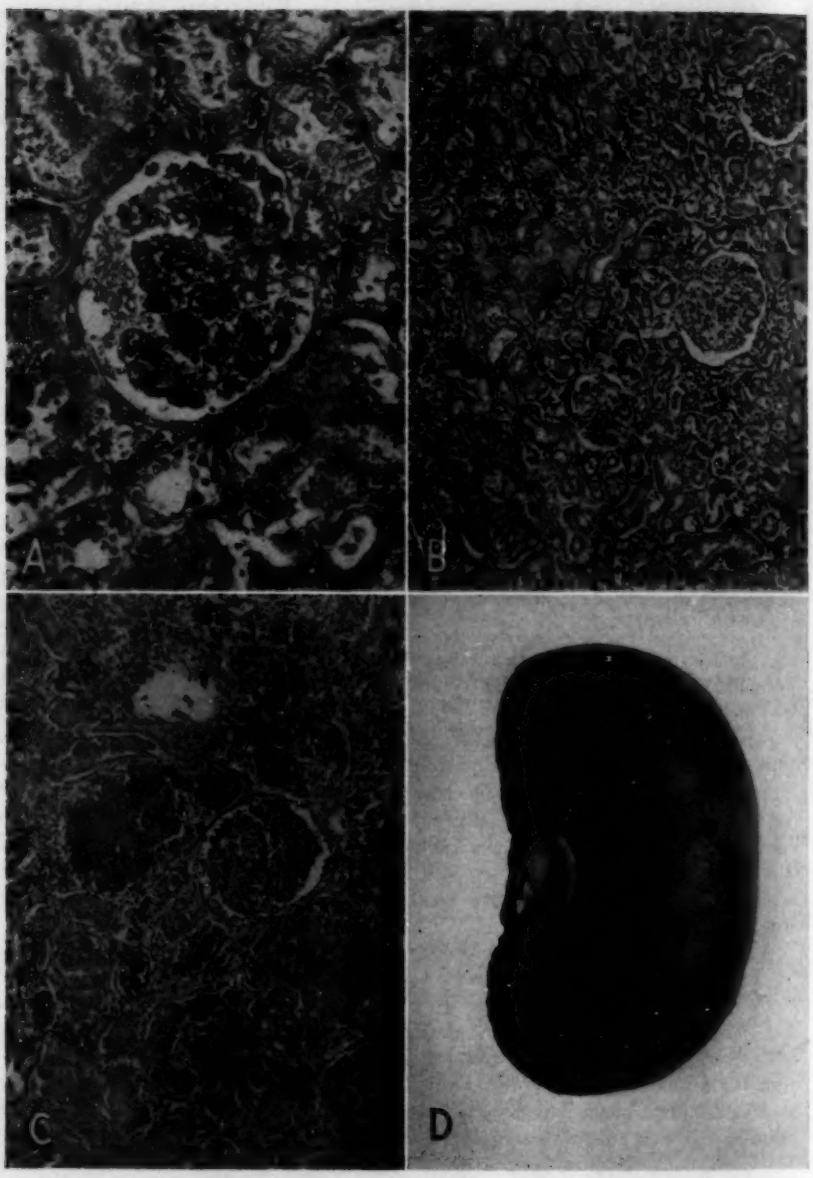

Fig. 1.—*A*, congested glomerulus with protein and some red blood cells in the capsular space. *B*, one well maintained glomerulus and a few maintained tubules in an area showing widespread glomerular and tubular necrosis. *C*, an area of infarction showing infarcted and well maintained glomeruli. *D*, gross appearance of an experimental renal lesion.

In sections showing the gross infarcts these were sharply demarcated from the surrounding parenchyma by a zone of congestion. The latter was located in well preserved parenchyma but was penetrated at various points by necrotic tubules, which extended out from the infarcted area. In this border area and just within the infarct was a narrow zone where polymorphonuclear leukocytes were seen in the intertubular stroma. The border took a tortuous course so that there were areas in which well maintained glomeruli were surrounded by necrotic ones. In the cortex corticis (Clara [12]) zone, maintained renal tissue was observed only at the extreme borders of the areas of gross infarction. The central portion of the cortical zone of the infarct extended to the surface, involving glomeruli and tubules in the cortex corticis.

In the main area of infarction the renal parenchyma had been reduced to a feebly acid-staning mass, in which the outlines of antecedent structure could still be made out. An interlobular artery in this area showed the process of homogenization of its wall but was filled with well maintained red blood cells. Throughout the rest of the area only a rare red blood cell was observed.

The medullary border of the infarct, external to the arcuate artery, showed an irregular zone in which the glomeruli were well preserved. Through this area and extending into the medulla were necrotic tubules which were continuous with the corresponding structures in the main area of infarction. Intermingled with these were other tubules, some of which appeared uninvolved whereas others showed endothelial-like epithelium, evidence of regeneration. This portion of the medulla was the site of intense congestion. The arcuate artery in this region contained a small unorganized nonoccluding thrombus. An interlobular branch of this artery showed a similar thrombus. The renal parenchyma supplied by this interlobular artery, however, showed no evidence of infarction.

Case 2.—A 68 year old man was in relatively good health until four months before admission to the surgical service of Dr. Ralph Colp. His illness began with a gradual onset of loss of weight and strength and progressive constipation. The caliber of the stool was observed to diminish, and there was occasional blood streaking. Three weeks before admission he noted defecatory urgency, tenesmus, and cramps of the lower part of the abdomen.

The patient was an elderly, poorly nourished white man. The lungs were clear and the heart not enlarged. The blood pressure was 120 systolic and 80 diastolic. There was moderate peripheral sclerosis. The abdomen was soft. The inguinal nodes were enlarged bilaterally, and there were bilateral indirect inguinal hernias. The liver was hard, and its inferior margin extended 4 cm. below the costal margin, occupying the epigastric region. Rectal examination showed an encircling indurated raised stenosing growth 3 inches (7.5 cm.) above the anus.

Examination on admission showed a 2 plus guaiac reaction in the stool. The hemoglobin was 85 per cent. The blood urea nitrogen was 16 mg., and the blood sugar 90 mg., per hundred cubic centimeters. The urine the day after admission was clear, with a specific gravity of 1.010. No albumin, sugar, acetone or bile was present. The microscopic examination gave negative results. Sigmoidoscopic examination confirmed the diagnosis of a stenosing new growth, and biopsy of the lesion showed adenocarcinoma.

At operation hepatic metastases were found, and sigmoid colostomy was performed. One week later the colostomy wound was opened. Twenty-four hours after the first operation a bed sore commenced to develop. The temperature became

12. Clara, M.: Arch. f. Kreislaufforsch. **3**:42, 1938.

irregularly elevated, varying from 99 to 102 F. There was a moderate amount of postoperative vomiting. Six days after operation singultus appeared, which was fairly severe and persistent. In the week preceding the opening of the colostomy wound, the fluid intake amounted to an average of 1,100 cc. daily. The urinary output averaged 1,400 cc. daily. In the twenty-four hours following the opening of the colostomy wound the fluid intake rose to 3,100 cc., but the urinary output fell to 670 cc. In the three days preceding death the fluid intake approximated 1,300 cc. and the output 420 cc. daily.

Three days after the opening of the colostomy wound acute pulmonary edema developed. At this time the pulse rate, which had ranged between 96 and 120, suddenly rose to 140 and to 160, with a definite change in its quality. The patient became pallid, and profuse diaphoresis developed. He lapsed into an unresponsive state. His respirations increased to 36 per minute. He remained in this condition for thirty-two hours before death. He died eleven days after the first operation, the temperature reaching 104.4 F. the day of death.

Autopsy was performed ten hours after death. The heart weighed 310 Gm. The epicardium showed a few pinhead-sized hemorrhages, and over the right auricle there were a few adherent tags. The free edge of the mitral valve was slightly thickened, and the anterior cusp was studded with lipoid flecks. Several of the chordae tendineae were thickened, but they inserted normally. There was moderate narrowing of the coronary arteries by yellow arteriosclerotic plaques. There were no endocardial thrombi. The lungs together weighed 1,400 Gm. Both pleural cavities were free from fluid and adhesions. The upper lobes of the lungs were congested and edematous. In the lower portions of the left upper lobe and the major portions of the bases of both lungs were areas of bronchopneumonia. The intervening parenchyma was deeply congested, but there was no evidence of pulmonary embolization. From the smaller branches of the bronchi to the lower lobes greenish yellow exudate could be expressed. A smear revealed gram-positive cocci in clumps, pairs and short chains, as well as gram-positive rods.

The abdomen was scaphoid, and the operative wounds showed no evidence of inflammation except directly about the suture material. The peritoneal cavity was clean. The stomach was distended with bile-tinged fluid. The small intestine and the ascending and transverse portions of the colon were moderately distended, and the musculature of the sigmoid colon appeared moderately thickened. Both limbs of the sigmoidostomy opening easily admitted the examiner's finger. Approximately 20 cm. from the anal orifice was a constricting annular carcinoma, adherent to the posterior wall of the bladder. The mucosal surface of the tumor was ulcerated. No grossly involved lymph nodes were recognized. There were anal varices, one of which was thrombosed. The liver weighed 2,400 Gm. It was congested, and about one half of the parenchyma was replaced by yellow, firm nodules of tumor tissue. The spleen weighed 170 Gm.; the pulp was fairly soft and of a dark purple-gray color, and showed distinct follicles. The pancreas was congested and showed normal lobulation. The bone marrow was without significant gross change.

The kidneys weighed 250 Gm. together. The capsules stripped with ease. The surfaces were smooth except for a few irregular pittings. Several triangular areas, averaging 1 to 1.5 cm. on a side, were distinguished from the remaining parenchyma by their light grayish-yellow color. The medulla was fairly well differentiated from the cortex. The glomeruli were seen as dark red dots. The pelves were of normal size but were markedly injected and mottled with pinhead-

sized hemorrhages, which extended into the minor calices. Smears of the pelves showed numerous gram-positive cocci in pairs and short chains. The hemorrhagic mottling extended to the upper third of both ureters. The remainder of the ureters showed nothing unusual. The urinary bladder was distended to 15 cm. in length with clear yellow urine. The prostate was slightly enlarged.

Microscopically the heart showed focal areas of congestion with diapedesis of red blood cells and leukocytes between the muscle bundles. The mitral valve was thickened and vascularized. The lungs showed extensive bronchopneumonia and areas of mild pneumonia with severe edema and congestion. There was a considerable amount of fibrin in the exudate, and a few pulmonary arterial emboli without organization were present. There was hemorrhagic bronchitis of the bronchi of the lower lobes. No pertinent information was gained from a study of the thyroid, gallbladder, pancreas, adrenals, prostate, testis or bone marrow. The stomach showed mucosal and submucosal congestion and partial occlusion of some serosal veins by unorganized fibrin thrombi. The sigmoid presented an infiltrating adenocarcinoma, which had metastasized to the regional lymph nodes, mesentery and liver. The rectum showed a hemorrhoidal vein with partial occlusion by a layered thrombus. The spleen revealed fragmentation. There was very conspicuous congestion. The large cells with vesicular nuclei and a small amount of slightly basophilic cytoplasm seen in infectious splenic softening were numerous here.

A low power study of the area of gross involvement in the kidney disclosed a central area of infarction similar to that described in the previous case. Here the renal parenchyma and stroma appeared as pale acid-staining ghost structures. Nuclei were gone in some places and were pale in others. Occasionally, either the tubular or the glomerular nuclei were well maintained in spite of the striking cytoplasmic changes. The area was largely without red blood cells, although an occasional large vessel contained blood in its lumen. Near the periphery of this main area of infarction leukocytic infiltration of the stroma was conspicuous. There was a narrow surface rim of relatively normal renal parenchyma maintained directly beneath the capsule.

The major infarct presented a wedge-shaped area of well maintained glomeruli and tubules, which projected deep into the cortex, with its base on the surface of the kidney. The opposite free border of the main infarct showed a gradual transition into a honeycombed arrangement of necrotic glomeruli and tubules intermingled with many which were well maintained. Regenerating tubular epithelium was seen among these tubules. There was also considerable congestion. No thrombosis or embolism was seen, and some of the arteries extending into the areas of both partial and relatively complete necrosis were blood filled, although their walls were involved in the general process of necrosis. Another section of an infarcted area showed a large interlobar artery containing a nonadherent thrombus. All the branches, however, were free from thrombosis or embolism, and many were blood filled.

The kidneys revealed in addition to the acute changes moderate arteriosclerotic changes. There was subendothelial proliferation in the smaller arteries, with some narrowing of the lumens and with associated areas of round cell infiltration and slight scar formation, and an occasional hyalinized glomerulus. The pelves showed very severe congestion but no evidence of acute inflammation or bacteria. There were chronic inflammatory changes in the peripelvic fat tissue, with one area of marked leukocytic infiltration.

COMMENT

There can be no doubt that the foci of necrosis in the kidney were the result of closure of one or more renal vessels. Hitherto, we have assumed that the type of lesion described has been due to organic closure of a large branch of the renal artery. This was the original interpretation made in the cases reported in the foregoing pages, despite the fact that no source for an embolus could be found. Furthermore, the finding of small nonocclusive thrombi within the lumen of an interlobar, arcuate or interlobular artery seems to lend support to that idea. However, as we have mentioned, the interlobular artery which showed a thrombus supplied an area of viable renal parenchyma. Similarly, the arcuate artery in which a nonocclusive thrombus was observed showed branches which were well filled with blood, and the same is true of the interlobar artery which was likewise affected. These observations cast doubt on the significance of these thrombi for the origin of the observed anemic infarcts. This doubt was intensified by the observation of a well filled interlobular artery containing well preserved red blood cells lying in the midst of an area of coagulative necrosis, which involved its outer walls. The media and adventitia of vessels of this size derive their blood supply from that of the surrounding tissues. It is obvious, therefore, that the cessation of blood flow which caused the necrosis of the vessel wall must have occurred in vessels which were branches of the interlobular artery. Further evidence in support of this concept is offered by the observation of relatively well maintained glomeruli located in the midst of an area otherwise completely infarcted (fig. 1 *B* and *C*). In addition, we have observed isolated glomeruli showing varying degrees of necrosis in which there was present no organic obstruction to the blood flow which could be demonstrated post mortem. Since Litten's experimental work [13] it has been well known that occlusion of a branch of the renal artery manifests itself by the presence of protein in the glomerular capsular space. This occurs as early as two hours after ligation of a branch of the renal artery. Occlusion of such a vessel for a longer time leads to progressive necrobiotic changes, which appear first and most obviously in the convoluted tubules. Striking morphologic alterations in the glomerular epithelium and endothelium occur only after ischemia of many hours' duration. This, however, is not to be considered as evidence against the presence of changes in the constituents of the tufts, for alteration in their function occurs as the earliest reaction to ischemia. This lack of early demonstrable changes in the glomerular tuft merely reflects our inability to detect them morphologically.

13. Litten, M.: Virchows Arch. f. path. Anat. **83**:508, 1881.

Clinically, both of these patients were in a state of shock for some time before death. In the first patient this was due to diffuse peritonitis. In the second, shock came on thirty-two hours before death and was evidenced by a sudden rise in pulse rate to 160 per minute, profuse diaphoresis, pallor, mental confusion and sudden diminution in urinary output in spite of an adequate intake. This observation is further supported by the presence in the first patient of gastric and jejunal lesions such as we have previously observed to occur in shock. The vasomotor reactions occurring in shock have been reviewed elsewhere [14] so far as they are applicable to the gastrointestinal tract. It has been known for many years that under certan conditions the afferent arterioles to the glomeruli are sensitive to the presence of epinephrine circulating in the blood. This Richards and his collaborators [15] showed to be true by direct observation of the vessels in the frog's kidney. Our experimental observations, which will be detailed, indicate that under the conditions of the experiments the site of vascular contraction in response to epinephrine is similarly located in the dog. The diffuse stimulation of the sympathetic nervous system which causes the vascular response in shock was sufficiently intense to have caused an intestinal lesion in case 1. That a similar response occurred in the kidney is indicated by the finding of numerous scattered, isolated infarcted nephrons. The anatomic observations lead one to the conclusion that the larger areas of infarction which were observed were the result of the fusion of many individually infarcted nephrons.

EXPERIMENTS

As already mentioned, we first observed the renal infarctions in our studies on the production of ulcerations of the digestive tract in dogs. In these experiments we injected intraperitoneally from 0.3 to 0.5 mg. per kilogram of 1:1,000 epinephrine hydrochloride. This was done daily for from six to thirty days. In order to avoid the possibility that the epinephrine was absorbed directly through the serosa of the various viscera in the peritoneal cavity, we also used intrapleural injections of epinephrine hydrochloride. In the latter series the dose varied from 0.6 to 1.0 mg. per kilogram of dog. One additional dog received massive doses of epinephrine in oil, subcapsularly. These dogs reacted in the same fashion as did those which received the intraperitoneal injections. In all, 13 dogs were used. The experiments were terminated by intravenous injection of chloroform, and complete autopsies were made immediately.

14. Penner and Bernheim.[2] Juhel-Rénoy.[3]

15. Richards, A. N., and Schmidt, C. F.: Am. J. Physiol. **71**:178, 1924.

Results.—The intestinal changes have been reported elsewhere.[1] In general it may be said that dogs which presented gross intestinal lesions did not present gross renal lesions and vice versa. Focal areas of necrosis were also observed at times in the liver, spleen, pancreas and submaxillary gland.

Grossly, the affected kidneys were not changed in size. The surfaces were smooth, and in general the capsule stripped with ease. The kidneys showed occasional small hemorrhages and irregular hemorrhagic mottling, which varied in extent and usually occurred bilaterally but occasionally unilaterally. On section these dark red discolored areas were found to extend deep into the cortex, which was broken up by pale gray, sometimes friable adjacent cortical tissue into irregularly outlined regions. The capsule overlying some of these definite areas of infarction was adherent (fig. 1 *D*). The renal vessels, both arteries and veins, were patent and showed no abnormalities.

As in the ligation experiments, the earliest microscopic change noted in the kidneys of our experimental animals was the presence of a protein-containing fluid in the glomerular space. This was not present in all the glomeruli seen but occurred apparently in a haphazard fashion. This protein coagulum was seen in glomeruli whose structure was normal according to accepted standards. In a stage which we consider to be representative of a more severe grade of damage to the glomerulus, red blood cells were observed in the coagulum. Many of the glomeruli appeared to be distinctly larger in size than usual and filled out Bowman's capsule to the point where no capsular space could be made out.

A striking feature in some of the glomeruli was a distinct thickening of the capillary wall, most of which appeared to be due to enlargement of the epithelial covering of the loops. This thickening often involved all the loops of a glomerulus. However, not infrequently it was seen in only a small number of the loops of the glomerulus; then the thickened loops showed an absence of red blood cells in their lumens, which were usually filled with plasma. Glomeruli which showed these changes in the capillary loops invariably had protein contents in the capsular spaces and not infrequently red blood cells in addition.

A later stage of the process was shown in the development of necrobiotic changes in the capillary loops. This at first might have involved isolated loops in a given glomerulus, but we were able to observe progressive involvement up to complete necrosis of an entire glomerular tuft. At this stage the glomerulus consisted of a mass of eosinophilic material in which the outlines of previous structures were indicated by the shadows of endothelial nuclei, which were apparently the last to disappear.

A closer examination of the topographic relationship between the affected glomeruli and their vascular supply showed that the former were in no way dependent for their distribution on the interlobular arteries. Ischemic glomeruli with thickened loops such as have been described were found in close relationship to others which showed thin-walled capillary loops filled with red blood cells. By studying such glomeruli in serial sections it was found that the afferent arterioles of such ischemic and hyperemic glomeruli might take origin from a common interlobular artery (figs. 2 and 3) which was filled with red blood cells. In addition we found ischemic glomeruli whose afferent arterioles were filled with red blood cells up to the point of division into the primary glomerular branches. This was not infrequently the case in glomeruli which were the site of total necrosis.

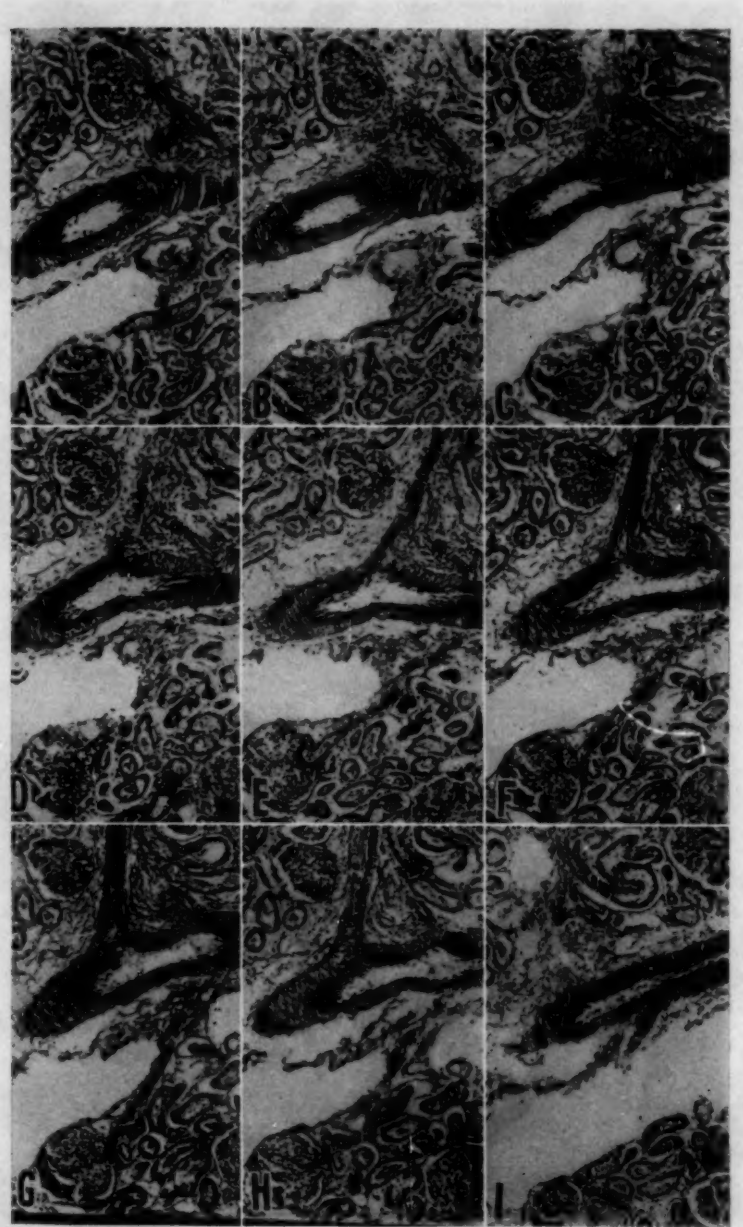

Fig. 2.—Serial sections showing a well maintained hyperemic glomerulus (above) and an ischemic, partially necrotic glomerulus (below). The afferent arterioles to both these glomeruli arise from the same interlobular artery.

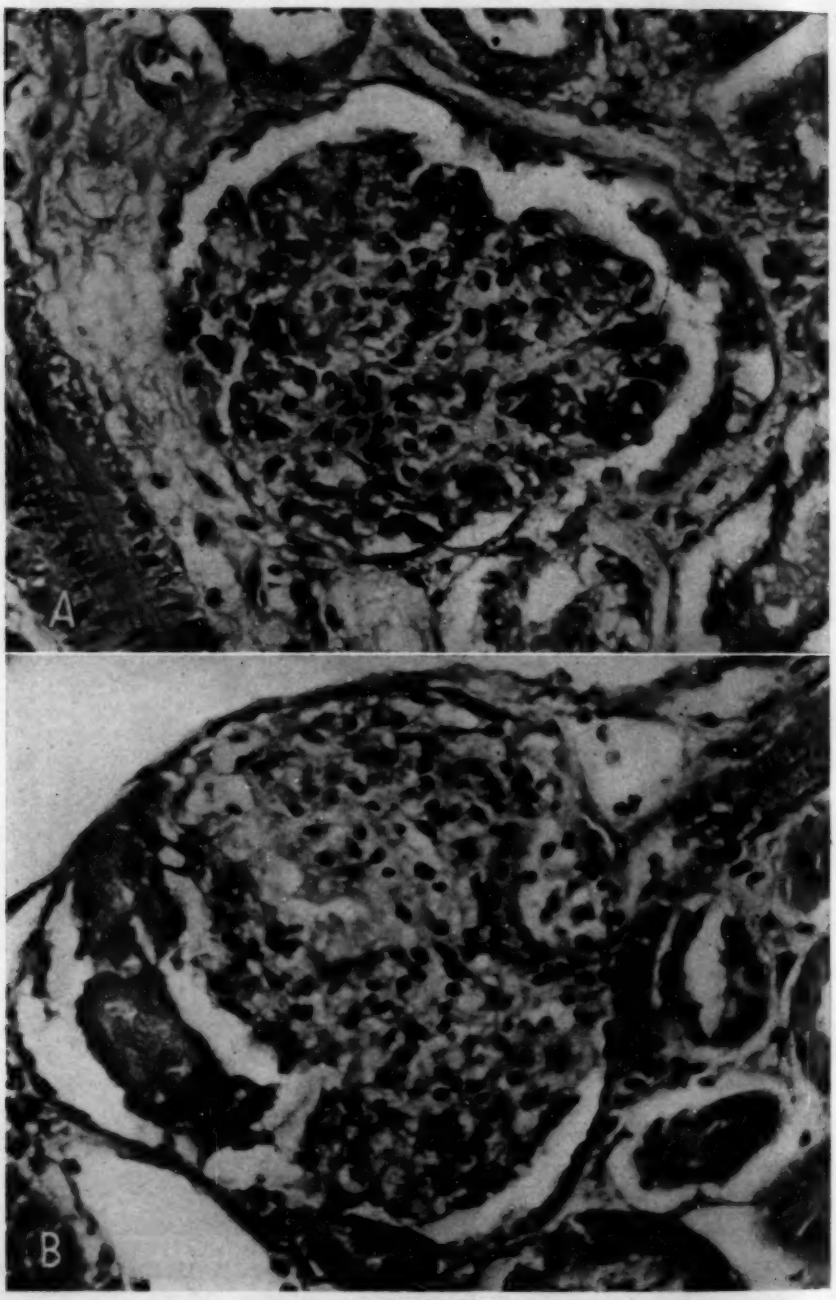

Fig. 3.—*A*, high power study of hyperemic glomerulus seen in figure 2. *B*, high power study of ischemic, partially necrotic glomerulus seen in figure 2.

In addition to the changes within the tuft itself the glomeruli not infrequently showed swelling of the epithlial cells lining their capsules. Many glomeruli showed adhesions between ischemic capillary loops and the swollen epithelium of the capsule. In rare glomeruli there seemed to be a focal increase in the number of capsular epithelial cells, which formed a structure resembling an epithelial crescent. Occasionally, a small segment of Bowman's capsule showed evidence of necrosis. When this involved only a part of the capsule, it occurred in contact with similarly necrotic loops of the glomerular tuft. In its most advanced stage the entire capsule and glomerular tuft were necrotic.

At the stage in which the glomeruli showed protein in the capsular space with tufts which appeared normal, the tubules in the corresponding areas likewise showed an eosinophilic protein in their lumens. At this stage no alterations could be made out in their epithelial cells. Somewhat later and corresponding to the glomeruli which were ischemic and whose capillary loops were thickened, the tubular epithelium showed deviations from the normal. These consisted in the appearance of extremely fine vacuoles in the cytoplasm as well as a gradual fading out of the nuclear chromatin material. Some of the nuclei, instead of fading out, became pyknotic. In addition to the protein contents of the tubules, which apparently originated in the glomeruli, there was found at this stage cellular debris derived from the lining of the tubules. In addition, some of the tubules contained red blood cells.

The stroma surrounding the glomeruli did not appear unusual in the earlier stages. However, there was definite edema of the stroma surrounding the larger arteries in the cortex. This edema was also found around the glomeruli and in the stroma between the tubules in the later stages of the process. By and large, the peritubular capillaries in the involved zones showed few red blood cells.

While many individual isolated glomeruli were observed in varying stages of the processes described, we also observed various-sized groups of such glomeruli. In some of the kidneys the fusion of these necrotic glomeruli resulted in the formation of areas of gross infarction, which we have already described.

Careful microscopic examination in serial sections showed the absence of any thrombi or emboli in the renal vessels.

Comment.—Our experimental procedure was such as to exclude any but a vasospastic mechanism as the cause of the lesions which we have described. The location of the exact site of this vasospasm was indicated by the experiments of Richards,[15] mentioned earlier. Our anatomic observations add support to the physiologic demonstration that under certain conditions the spasm takes place in the afferent arterioles. Furthermore, the finding of infarcted glomeruli whose afferent arterioles were blood filled up to their point of primary division agrees with the observations of Richards and others that there is a regulatory mechanism for the blood flow through the glomerulus located at this point.

It is also of interest that the unit of renal structure affected was the nephron. While the morphologic changes in the glomerulus are more difficult to determine, there is no doubt that the first event consists in an increase in the permeability of the capillary loops. In analogy with our findings in the case of the gastrointestinal tract, we visualize this as being the effect of ischemia and anoxemia on the endothelium

and epithelium of the glomerular capillaries. At this stage we have been unable to detect any morphologic changes in the tufts. It is only when the ischemia has persisted for a somewhat longer period that we are able to detect swelling of the epithelial cells, which initiates the sequence of events leading to total necrosis. The same is true of the tubules, in which, however, morphologic alterations are more readily detected. It is for this reason that the tubules have always been considered to be more sensitive to damage than the glomeruli.

SUMMARY

In the course of experiments intended to reproduce the homeostatic vasomotor mechanism occurring in shock we unexpectedly observed gross renal lesions closely resembling bilateral cortical necrosis of the kidneys as seen in man. This led us to compare these two lesions more closely. This was done by studying casuistic reports from the literature in which such lesions had been described in a variety of clinical states. In addition, we have studied 2 cases of our own which fall into a similar category. While we do not claim that bilateral cortical necrosis of the kidneys has a single genesis in all cases, a review of the clinical features of these cases shows that a profound state of shock was present often for days before death occurred. In the absence of evidence of either embolization or a focus from which emboli could have been discharged we hold that the vasospasm which occurs in shock is of sufficient intensity and duration to result in these lesions. The description of intestinal lesions in the cases of Helwig and Schutz, as well as in 1 of our cases, lends support to this contention. These lesions have been found in association with shock of the most varied causation.

HISTOLOGY OF EXPERIMENTAL APPENDICAL OBSTRUCTION (RABBIT, APE AND MAN)

RAYMOND E. BUIRGE,* M.D.

CLARENCE DENNIS, M.D.

RICHARD L. VARCO, M.D.

AND

OWEN H. WANGENSTEEN, M.D.

MINNEAPOLIS

The secretory capacity of the cecal appendage of the rabbit and of the vermiform appendix in the chimpanzee and man has been described.[1] Perforation was found to be a fairly constant sequel to luminal obstruction of the cecal appendage of the rabbit. The great secretory capacity of this appendage in the rabbit is indicated in the observation that in 20 animals the average amount of fluid collected after six hours of observation was 20 cc. per animal. Of 22 exteriorized vermiform appendixes in man, 19 afforded evidence of fluid secretion attending obstruction. No secretory pressure developed in 3 of the 22 appendixes obstructed and subjected to appendicostomy. In one of these the appendix had a lumen, but microscopic examination showed no evidence of a normal mucosa. In another the blood supply of the appendix had been compromised during the procedure of exteriorization, and consequently the negative result was essentially without significance. In the third instance the cannula had not entered the lumen, and no secretory pressure was recorded. In those that secreted, 1 to 2 cc. was collected daily. Perforation attended obstruction of the vermiform appendix in the chimpanzee. In the gibbon, monkey and many other animal species, no evidence of fluid secretion was obtained, and perforation did not attend the establishment of luminal obstruction.

PURPOSE

This study is made with the consideration in mind of evaluating the nature of the histologic reaction attending luminal obstruction in those

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* At present holder of National Cancer Research Traineeship.

From the Department of Surgery of the Medical School of the University of Minnesota.

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1. Wangensteen, O. H.: Proc. Inst. Med. Chicago **12**:266, 1939.

instances (man, chimpanzee and rabbit) in which evidence of fluid secretion occurs. It is particularly desirable to know whether induced obstruction in the exteriorized appendix of man resembles the histologic picture observed in spontaneous appendicitis.

SOURCE OF MATERIAL

The cecal appendage was studied in 160 rabbits subjected to various procedures incidental to complete obstruction of the appendical lumen by ligature. Nine unobstructed controls were added to this series. In addition, 21 normal cecal appendages were studied (fig. 1). For purposes of cytologic orientation, the reports of Downey,[2] Evans,[3] Howard and Perkins,[4] Ringoen[5] and especially Latta[6] were found helpful.

The cecal appendages of 2 gibbons and 3 chimpanzees were studied microscopically after they had been obstructed, incannulated and exteriorized for various lengths of time. Through the cooperation of Dr. George A. Barnett, of Chicago, the normal excised vermiform appendixes of 4 chimpanzees were made available for histologic examination.

In addition to 27 normal, or inactive, human appendixes, removed during other operative procedures, 22 exteriorized, obstructed appendixes were available for examination in 22 patients in whom obstruction followed by appendicostomy was performed at the time that colostomy was done for carcinoma of the colon. This material provided an opportunity to study the inflammatory reaction attending ligature obstruction of the vermiform appendix in man, compared with that of the chimpanzee, the gibbon and the rabbit.

METHOD OF STUDY

In the present study a large part of the material used was promptly fixed in 4 per cent solution of formaldehyde after removal from the living animal or shortly after death. Five specimens were excluded because of the possible effects of postmortem change. Circular blocks of tissue were taken through the area of rupture in the ruptured appendix and usually from the middle third of the unruptured appendix. In many instances blocks of tissue were also taken proximal to the site of obstruction and also through the distal third of the appendage. At least three to six microscopic sections, 7 microns thick, were made from each block. Some blocks were cut serially, using every fifth section until twenty to forty sections had been utilized. All of the sections were stained with hematoxylin-eosin stain. Many sections were stained by the Gram-Weigert method for bacteria, and a few connective tissue spreads, as described by Kolouch,[7] were stained by Giemsa's method.

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2. Downey, H.: Folia haemat. **19**:148, 1915.
3. Evans, H. M.: Am. J. Physiol. **37**:243, 1915.
4. Howard, W. T., Jr., and Perkins, R. G.: Johns Hopkins Hosp. Rep. **10**: 248, 1902.
5. Ringoen, A. R.: Anat. Rec. **9**:683, 1915.
6. Latta, J. S.: Am. J. Anat. **29**:159, 1921.
7. Kolouch, F., Jr.: Am. J. Path. **15**:413, 1939.

CRITERIA OF DIAGNOSIS

The varied macroscopic changes observed in these specimens included vascular congestion, hemorrhage, edema, distention, change in thickness of the wall, gangrene, rupture and local or general peritonitis.

A histologic diagnosis of acute inflammatory change was made only when polymorphonuclear granulocytes were found in the field of inflammation. Examination of many sections showed that the site of inflamma-

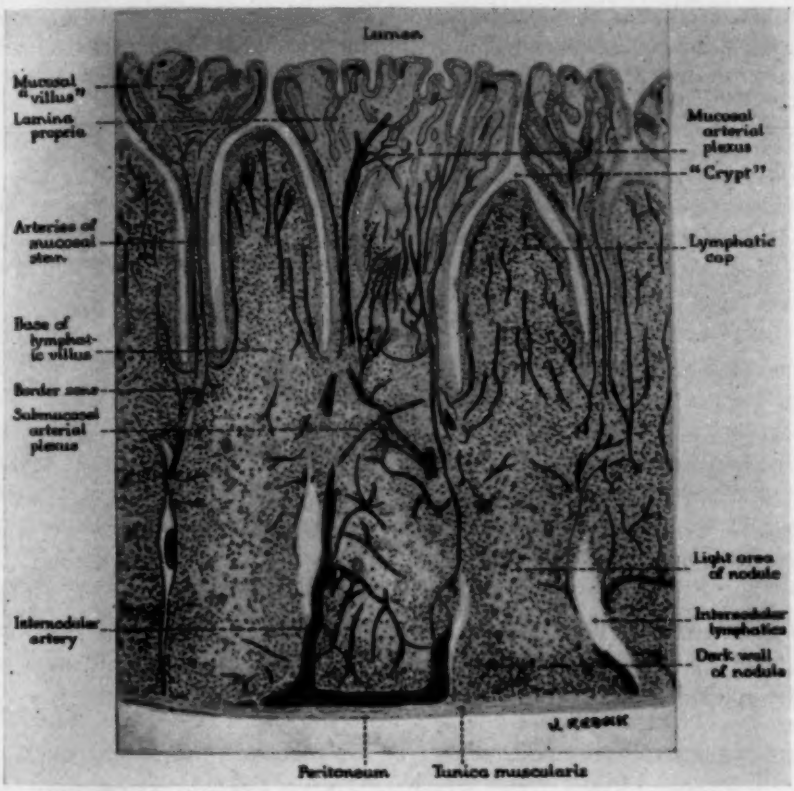

Fig. 1.—Rabbit. Photomicrograph of an artist's sketch through a section of the cecal appendage. Intra-arterial injection of gelatin carmine. (Drawn by John Rebuck, Department of Anatomy, University of Minnesota.)

tory field varied as well as the degree of reaction; therefore it was deemed advisable, if for no other purpose than statistical arrangements, to provide some classification of the inflammatory process. In using the accompanying histologic classification of experimental appendicitis no effort was made to take into consideration such factors as procedure, time, virulence of associated invading organisms or the anatomic pecu-

liarities of the appendix affected. It is a classification for the purpose of describing the pathologic stages encountered in this series of experiments. The various histologic stages pass quite imperceptibly into each other and, to a degree, any two or all of them may be present; however, the classification provided an orderly arrangement for a consideration of the inflammatory changes noted. A classification of the various stages of inflammation in the appendix is not entirely satisfactory, for there is no definite line dividing one stage from another. It should be emphasized that the localization of the cellular reactions to any one layer is by no means a frequent finding, even though the predominant

TABLE 1.—*Histologic Classification of Parietal Appendicitis*

I.	Serosal lesions
	Grade 1. Granulocytes in serosa and tela submucosa
	Grade 2. Granulocytes in serosa, muscularis and submucosa
II.	Mucosal appendicitis
	Group A. Acute inflammatory change in mucosa and active proliferation in lymphatic nodules
	Grade 1. Granulocytes limited to mucosa
	Grade 2. Granulocytes in mucosa and serosa
	Grade 3. Granulocytes in mucosa, serosa and muscularis
	Group B. Infarction and necrosis of mucosa, with associated lymphadenitis
	Grade 1. Proliferation of mononuclear exudate cells; inflammatory macrophages in lymphatic nodule and serosal layers
	Grade 2. Granulocytes in serosa
	Grade 3. Granulocytes in muscularis
	Grade 4. Granulocytes in muscularis and serosa
III.	Diffuse appendicitis
	Grade 1. Granulocytes in all layers except deep in lymphatic nodule
	Grade 2. Granulocytes in all layers and deep in lymphatic nodule
IV.	Healing appendicitis

anatomic change concerned that layer. The accompanying classification (table 1) is of a topographic order and utilizes the anatomic areas of the appendix invaded by polymorphonuclear leukocytes.

CLASSIFICATION ON BASIS OF MICROSCOPIC OBSERVATIONS

I. *Serosal Lesions.*—By serosal appendicitis is meant an inflammatory process affecting only the serosa and muscularis of the appendix. Histologically, the superficial blood vessels, both those immediately below the peritoneum and the deep subserosal vessels, are intensely congested and tortuous. There is a loss of the normal sheen of the serous covering. The presence in all the layers of small and large interstitial hemorrhages is a common finding in experimental obstructive appendicitis. There is often intense edema, which in some areas is out of proportion to the other changes. The serosal lesions are divided according to the presence or absence of polymorphonuclear leukocytes in the muscularis.

Grade 1. The minimal reaction of the serosa is depicted by the extravascular presence of polymorphonuclear granulocytes in the subserosal and submucosal areas, where the leukocytes have infiltrated along the course of the blood vessels, especially immediately under the muscularis in the interfollicular zone.

Grade 2. In this group the muscular layer shares to a variable extent in the reaction just described (grade 1), with a leukocytic infiltration separating the muscle fibers, which show more or less degenerative changes. The leukocytic infiltration is most marked about the vascular hiatuses, appearing frequently like microscopic abscesses. At this stage the mucosa is generally intact but stains cloudily, and in the areas of the lymphatic villus there may be increased exfoliation of epithelium and lymphocytes into the appendical lumen.

II. *Mucosal Appendicitis.*—This division is characterized essentially by the inflammatory process affecting the mucous lining of the appendix to such a degree that it overshadows the inflammatory reaction elsewhere in the appendical wall.

Group A. The gland epithelium shows active proliferation and increased secretion, and there are congestion and edema in some areas, with degeneration of the epithelium. The glands often appear compressed and thinned out owing to the increased intraluminal and interstitial tension. There may be effusion of blood and fluid under the mucosa. The lymphatic nodules have participated in the reaction by an increase in the size and number of the germinal centers (light zones) containing large mononuclear phagocytes. The abundant pale cytoplasm of the macrophage gives to the germinal center a light, vacuolated appearance. Many of the polyblasts contain ingested granulocytes, the nuclei of which assist in their identification. In frequent instances the mucosa alone is infiltrated by leukocytes, but this is only a momentary stage, for shortly other layers are concerned, as indicated in the following divisions.

Grade 1. The presence of polymorphonuclear leukocytes in the mucosa is designated as grade 1 mucosal appendicitis.

Grade 2. This indicates granulocytes in the mucosa and serosa.

Grade 3. Granulocytes are present in the serosa, muscularis and mucosa.

Group B. This group was required because in a number of instances the mucosa was severely damaged by infarction and necrosis.

Grade 1. This includes a few appendixes found to have infarcted mucosa and a predominating proliferation of mononuclear exudate cells (polyblast of Maximow[8]), especially in the lymphatic nodule.

8. Maximow, A.: Arch. Path. **4**:557, 1927; Arch. f. exper. Zellforsch. **5**:169, 1927.

Grades 2, 3 and 4. These include the appendixes found with a mucosal change characteristic of group B and lymphadenitis in addition to the presence of granulocytes in the serosa (grade 2), in the muscularis (grade 3) and in both the serosa and muscularis (grade 4).

III. *Diffuse Appendicitis.*—Grade 1. The whole appendix shows inflammatory reaction. The blood vessels are engorged, the tissue is highly edematous, and there is general cellular proliferation in all the layers. The mucosa, submucosa and muscularis share in the leukocytic reaction.

Grade 2. This includes appendixes which in addition have suppurative lymphadenitis, indicated by the presence of a variable number of polymorphonuclear granulocytes in the lymphatic nodule, sometimes forming miliary abscesses. Occasionally the central portions of the nodule are necrotic. The nodule may open on the mucous membrane, extruding its contents into the appendical lumen.

IV. *Healing Appendicitis.*—This group includes those appendixes in which cytologic evidence of acute inflammation is absent in all the layers; however, the presence of fibroblasts with a varying degree of fibrosis indicates the previous presence of an infection.

RESULTS IN RABBITS

1. *Control Series.*—Nine rabbits were used. The appendages from 2 were normal following anesthesia induced with an intravenous injection of pentobarbital sodium. After anesthesia, celiotomy and appendectomy, 1 appendage showed edema of the mucosa and hemorrhage: 1 was normal following an injection of india ink into the appendical lumen; while 2 unobstructed cecal appendages, following insertion of a balloon into the lumen and electrical stimulation, had mild serositis after a two hour period of trauma. Two unobstructed appendages subjected to rough manipulation had mild acute mucosal appendicitis six and eight hours after the trauma. One incannulated and washed but not obstructed specimen (ligature placed about the base) had mild traumatic serositis (fig. 2) after ten hours. Trauma may result in the histologic picture of mild appendicitis; however, the usual surgical procedure employed in these experiments incites a serosal reaction which results infrequently in leukocytic infiltration of the muscular layer of the appendage. Gangrene of the tissues or rupture was not encountered in the controls or unobstructed appendages.

2. *Obstruction of Unwashed Cecal Appendage.*—Twenty-six cecal appendages were obstructed, 17 at the base, 7 proximal to the base and 2 distal to the base, by avascular ligation. Of these, 24 showed evidence of acute inflammation, while 1 obstructed for four hours and 1 obstructed for seven hours showed serositis. One rabbit died eight days later with a ruptured appendage and generalized peritonitis; the sections showed no evidence of acute inflammatory change. Twelve appendages with acute appendicitis had ruptured, with a varied degree of periappendical involvement.

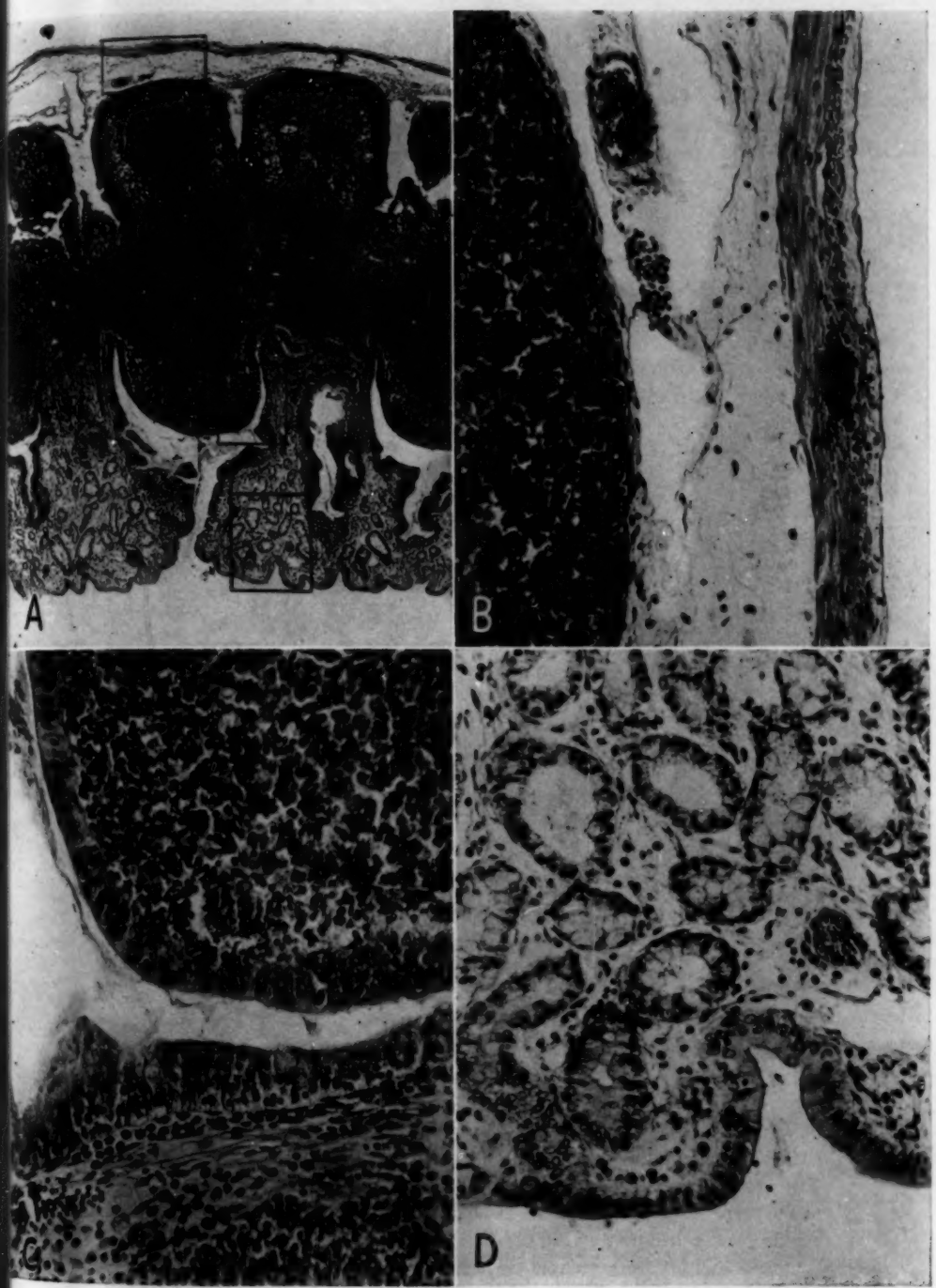

Fig. 2.—Rabbit (control). Celiotomy, incannulation, application of ligature loosely about the base of the appendage, which was not obstructed. Photomicrographs. *A*, normal architectural outline of a circular section through the appendical wall; × 57. *B*, edema present under the serosa and muscularis; × 143. *C*, no reactive changes present in the lymphatic villus or in the borderline area; × 143. *D*, mucosa free of any proliferative changes and lymph spaces somewhat widened; × 143. Traumatic serositis.

3. *Obstruction of Washed Cecal Appendage.*—In 5 rabbits the appendical lumen was irrigated through a cecostomy; in 1 instance a glass cannula was used and the system connected to a revolving kymograph. A pressure of 80 cm. was attained twenty-three and a half hours after obstruction, when spontaneous rupture occurred. The 5 appendages showed evidence of acute inflammation, 2 with gangrene and 2 with rupture (fig. 3).

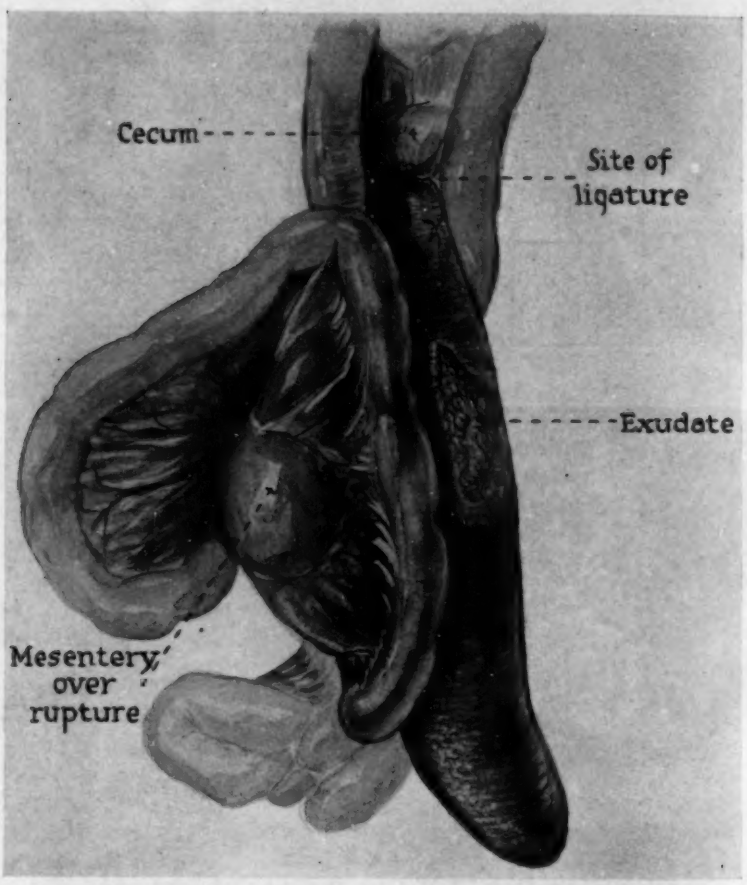

Fig. 3.—Rabbit. Photograph of an artist's sketch depicting the gross anatomic changes found at reoperation nine days after obstruction of the cecal appendage. The appendage had ruptured, and the site of perforation was sealed over with mesentery. The appendage was distended and filled with clear fluid. There was evidence of generalized peritonitis. Microscopically, the wall was thinned, the lymphoid follicles were reduced in size, and many had emptied their contents into the appendical lumen. Polymorphonuclear leukocytes were not found in the wall. There was fibrosis in all layers of the appendical wall. The histologic diagnosis was healing appendicitis.

4. *Appendical Obstruction of Three and a Half and Six Hours' Duration.*—In 15 rabbits (table 2) a ligature tied 1.5 cm. proximal to the base of the appendage over a short rubber tube was released after a period of complete obstruction, and appendectomy was performed at intervals following the release of the obstruction. Two specimens at the end of three and a half hours and 4 at the end of six hours of obstruction (2 of these had perforated) appeared distended, edematous and congested; the microscopic change at this time concerned the serosa only. The degree of distention was indicated by the measured diameter of the appendical wall and lumen at the true base.

TABLE 2.—*Results Attending Release of a Proximally Placed Ligature After a Period of Obstruction of the Unwashed Cecal Appendage of the Rabbit*

	Interval of Obstruction		Release of Obstruction		
Rabbit	Duration of Obstruction, Hr.	Diameter of Appendical Base at Time of Release of Obstruction, Mm.	Hours After Release of Obstruction That Appendectomy Was Performed, Hr.	Diameter of Appendical Base at Time of Removal of Cecal Appendage, Mm.	Histologic Diagnosis
S1R1	3.5	24.0	Immediately	15.0	Serosal appendicitis, grade 1
S1R3	3.5	26.0	Immediately	8.6	Serosal appendicitis, grade 1
S1R2	3.5	Not measured	4.0	10.4	Serosal appendicitis, grade 1
S1R4	3.5	24.0	8.0	8.0	Serosal appendicitis, grade 1
S1R5	3.5	15.0	24.0	8.7	Diffuse appendicitis, grade 2
S1R6	3.5	12.0	48.0	8.7	Serosal appendicitis, grade 1
S5R1	6.0	Ruptured	Immediately	...	Serosal appendicitis, grade 1
S5R5	6.0	22.0	Immediately	9.0	Serosal appendicitis, grade 1
S5R4	6.0	17.0	Immediately	8.5	Serosal appendicitis, grade 1
S5R2	6.0	Ruptured	Immediately	...	Serosal appendicitis, grade 1
S5R3	6.0	15.0	24.0	6.5	Serosal appendicitis, grade 1
S5R6	6.0	24.0	48.0	Specimen lost	

In 12 rabbits the cecal appendage was obstructed for an interval of three and a half hours and six hours, when the animal was reoperated on and the distention of the appendage determined by measuring the diameter of the appendage at its junction with the cecum. Careful measurements were made of the base area with calipers, then the obstructing mechanism was released. The diameter of the appendage was again determined after a varying interval following the release of the obstruction. The specimens were fixed, stained and mounted. Detailed micrometric measurements of the various layers of the appendical wall were unsatisfactory because of separation of the layers by marked edema, interstitial hemorrhage and rupture of the muscle fibers. However, measurements of the diameter of the appendical lumen and walls were obtained. The average diameter

of 9 specimens was 9.3 mm. In a previous study[9] measurements of the normal cecal appendage were made, including the musculature, the thickness of the wall, the diameter of the lumen and the diameter of the appendage, and the average diameter of 13 specimens was found to be 8.15 mm. In a recent series (Varco) of 20 specimens measurements of the diameter through the region of the base ranged from 8 to 12 mm., with an average of 9 mm. The average for the group of 33 specimens is 8.57 mm., which agrees with the average diameter of 9.3 mm. obtained for the group of appendages previously released from an obstructing mechanism. When the appendages were removed after release of the obstruction, they appeared nearly normal, and the microscopic picture showed minimal change. One specimen after three and a half hours of obstruction showed a diffuse appendicitis. It will be noted that the greatest diameter (average 20.2 mm.) of the appendage was observed after three and a half hours of obstruction. In fact, those cecal appendages obstructed for six hours were slightly smaller (average 19.5 mm.) in diameter.

TABLE 3.—*Histologic Diagnosis of Changes in the Washed, Obstructed, Incannulated Cecal Appendages*

	Experiments	Pressure, Cm. of Water
Serosal appendicitis, grade 2	1	18.5
Mucosal appendicitis, group B, grade 1	2	90, 66
Mucosal appendicitis, group B, grade 2	1	71
Mucosal appendicitis, group B, grade 4	4	102, 79, 52, 42
Diffuse appendicitis, grade 1	2	47.2, 85
Diffuse appendicitis, grade 2	2	65, 85
Total	12	

Eleven of the 12 appendages revealed, on histologic examination after release of the obstructing ligature, a mild serosal reaction. On the basis of such experimental evidence one might be permitted to surmise that spontaneous appendicitis, when caused by luminal obstruction, presents similar minimal histologic changes following release of the mechanism of obstruction.

5. *Measurement of Pressure Developed in Obstructed Appendages.*—In 12 rabbits the distal end of the appendage was incannulated, the lumen washed, the base ligated and the closed system connected to a recording kymograph. No constant relationship was noted between the duration of obstruction and the intraluminal pressure produced. Five experiments over a period of five hours had a range of 18.5 to 90 cm. of water. In five experiments the appendage was obstructed eight, nine, nine, ten and fourteen and a half hours, producing pressure changes of 52, 79, 71, 66 and 85 cm. of water, respectively.

6. *Effects Attending Administration of Drugs During Obstruction of Appendical Lumen.*—(*a*) Effects resulting from the administration of pilocarpine, epinephrine and pitressin were judged only in the light of histologic changes following obstruction, which was accompanied by an inflammatory reaction in the wall of 3 appendages.

9. Wangensteen, O. H.; Buirge, R. E.; Dennis, C., and Ritchie, W. P.: Ann. Surg. **106**:910, 1937.

(*b*) Croton oil was given to 11 rabbits at irregular intervals relative to the onset of obstruction. Nine of the appendages were unwashed. Two incannulated washed appendages ruptured. All sections revealed acute inflammation.

(*c*) Administration of magnesium sulfate and castor oil to 6 rabbits, by means of a small catheter introduced into the stomach after obstruction and incannulation of the washed cecal appendage was attended by acute appendicitis in all and rupture in 2.

(*d*) Hypertonic saline solution was injected intravenously at diverse times prior to and after obstruction of the appendical lumen in 18 rabbits. In a single instance a pressure of 136 cm. of water was attained in three hours, accompanied by rupture. All sections, regardless of the details of procedure, showed a degree of acute appendicitis. Four appendages ruptured.

7. *Effects Attending Incannulation and Obstruction of Lumen of Unwashed Appendix.*—In 5 rabbits acute changes were noted; 2 appendages ruptured, 1 was gangrenous, while 2 revealed only minimal changes.

TABLE 4.—*Histologic Diagnosis Attending Constant Intraluminal Pressure*

	Average Pressure, Cm.	Average Time, Hr.	Experiments
Serosal appendicitis, grade 1	17.8	15.6	6
Serosal appendicitis, grade 2	30.0	24.0	2
Mucosal appendicitis, group B, grade 1	28.5	16.0	2
Mucosal appendicitis, group B, grade 3	15.5	27.0	3
Mucosal appendicitis, group B, grade 4	30.0	24.0	2
Diffuse appendicitis, grade 1	17.0	20.0	3
Diffuse appendicitis, grade 2	31.5	31.5	2
Total			20

8. *Effects Attending Trauma of the Obstructed Cecal Appendage.*—Six rabbits treated according to Wells's [10] method of traumatizing the appendical wall and mucosa, by scratching with a small hypodermic needle inserted through the wall of the appendage into the lumen, showed, on removal at intervals following concomitant trauma and obstruction, acute appendicitis with complications; 3 were ruptured, 1 was gangrenous, and 1 at the end of thirty-eight days presented a mucocele of the appendage with fibrosis of the wall. In all the sections the greatest extent of the inflammatory reaction was in the area of trauma.

9. *Curettage of Mucosa.*—In 6 rabbits the mucosa was curetted and the appendage obstructed and incannulated. Perforation was noted in 2; 1 was gangrenous, and all revealed a severe grade of leukocytic infiltration of the appendical wall.

10. *Effects Attending Constant Intraluminal Pressure.*—Twenty rabbits were used to determine the histologic effects of sustained intraluminal pressure. In general, low pressure of long duration was often associated with minimal reactions, although acute reactions were found to occur with apparent indifference to time or pressure; while pressures over 15 cm. of water were frequently associated with acute inflammation.

11. *Intraperitoneal Collection of Appendical Fluid in a Balloon.*—In 3 rabbits the appendage was ligated at the base, and in 7 the ligature was placed 1.5 cm. proximal to the base, i. e., up on the cecum, and the lumen incannulated to an

10. Wells, A. Q.: Brit. J. Surg. **24**:96, 1937.

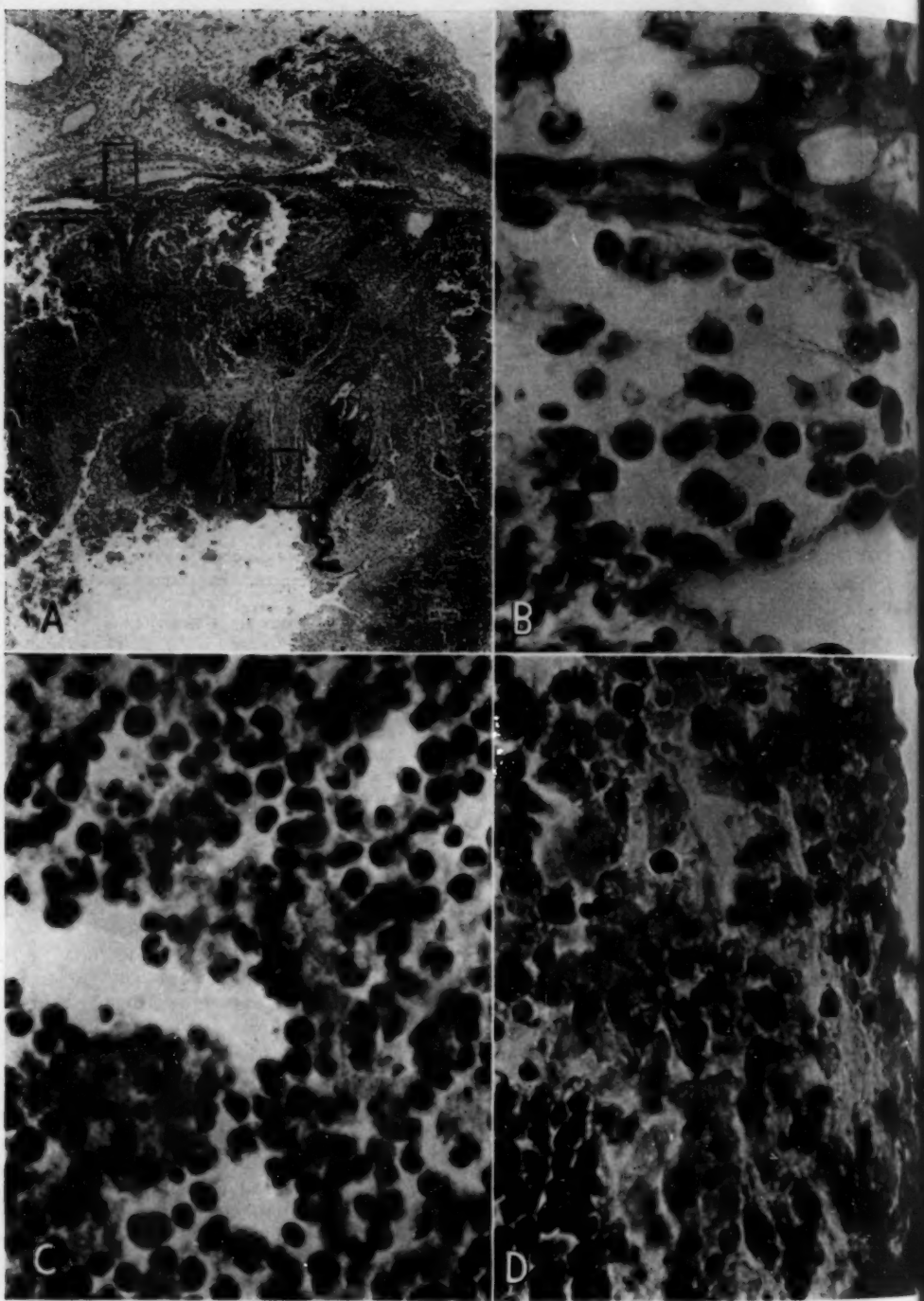

Fig. 4.—Rabbit. Photomicrographs showing the histologic reaction attending obstruction by ligature and incannulation of the appendical lumen. The Intraluminal pressure was not allowed to exceed 40 cm. The duration of the obstruction was thirty hours. *A*, inflammatory and early degenerative changes in all layers of the appendical wall; × 50. *B*, polymorphonuclear leukocytes in the muscularis; × 504. *C*, reactive changes within a lymphatic nodule, with infiltration by scattered polymorphonuclear leukocytes; × 504. *D*, early necrosis, compression of the glands and few scattered polymorphonuclear leukocytes in the mucosa; × 504. Diffuse appendicitis, grade 2.

attached, very thin distensible balloon. A thin serous fluid was collected usually, the *p*H of which ranged between 8.78 and 7.12 after six hours of obstruction. Perforation was noted in 2 appendages. A degree of acute inflammatory change was found in all the sections, with a diminution of the acute inflammation in areas removed from the site of obstruction.

12. *Results of Obstruction and Appendicostomy.*—In 9 rabbits, following the establishment of appendical obstruction, an external fistula was made by means of an appendicostomy. The secretion of fluid was found to attain a pressure of 14 cm. in one appendage after eleven days of drainage and 10 cm. in another after four days, with associated acute macroscopic changes. In 3 appendages after obstruction and appendicostomy, evidence of recent inflammatory changes or fibrosis was found in twenty-three, twenty-nine and thirty-four days, when the rabbits expired. Two animals, following spontaneous closure of the appendicostomy on the thirteenth and thirty-fifth postoperative days, expired sixty-one and seventy-five days after the establishment of the appendicostomy, with general peritonitis; no evidence of the appendage was found in 1 rabbit; in the other it was a necrotic slough. After one appendicostomy, at the end of thirty-six hours there was mucosal appendicitis, group B, grade 4. In 1 rabbit the proximal end of the appendage was exteriorized. At the end of forty-nine days the appendage was reduced to half its original length, but otherwise it appeared normal. Microscopically, the sections showed no evidence of acute inflammation, but there was considerable fibrosis in all the layers.

13. *Interference with Circulation of Cecal Appendage.*—(*a*) Arterial. In one experiment the appendical artery of a rabbit was included in the obstructing ligature, and the appendage was removed in eighteen hours. No fluid had been produced. Sections showed necrosis of the mucosa and acute changes in the remaining layers.

(*b*) Venous. The appendical vein was included in the ligature obstructing the appendage in another experiment. Fluid was slowly formed in the appendical lumen. The appendage ruptured and appeared gangrenous.

(*c*) Arterial and Venous Occlusion. In one experiment the appendical lumens of 2 rabbits were washed and incannulated and the artery and vein at the base included in the obstructing ligature. No fluid was produced, the appendage was congested, and histologically there was mucosal appendicitis, group B, grade 2.

In a second experiment the ligation of the appendical base included the artery and vein together with four vessels in the distal third of the ileoappendical mesentery. After a period of twenty-four hours the rabbit expired. The cecal appendage was not distended by intraluminal fluid. There was segmental gangrene, limited to the distal third. Microscopic sections revealed mucosal appendicitis, group B, grade 1.

In the third experiment the artery and vein at the base were ligated. The appendage was sectioned at the base, the tip of the cecum inverted and the proximal portion of the appendage exteriorized through a stab wound. At the end of forty-nine days the cecal appendage was half its former size, and microscopically it revealed marked fibrosis in all the layers.

14. *Bacteria in the Tissues.*—Bacteria, identified by the Gram-Weigert method, were found in the appendical tissue removed from normal rabbits. Ribbert,[11]

11. Ribbert, H.: Virchows Arch. f. path. Anat. **132**:66, 1893.

Bizzozero[12] and Ghon and Namba[13] reported similar observations. Organisms were also found in obstructed appendages of rabbits. Bacteria were noted in increased numbers in gangrenous specimens. Altogether, 21 normal and 76 obstructed rabbit appendages examined showed the presence of bacteria.

OBSTRUCTION OF VERMIFORM CECAL APPENDAGE IN GIBBONS

The details of establishing obstruction and incannulation of the exteriorized appendix of the gibbon, chimpanzee and man have been described.[14] In the first gibbon a pressure of 19 cm. was gradually attained over a five hour interval of obstruction; it then fell slowly to from 0 to 5 cm. of water, where it stabilized for the remainder of the experiment. An appendical pressure of 18 cm. developed in the second gibbon in three hours, and was followed by a gradual fall to zero, the pressure remaining at zero during the last eight hours of the twenty-two hour period of obstruction. The appendixes of both gibbons showed in sections traumatic serositis, which in one involved the muscularis. The failure of a sustained intraluminal appendical pressure without accompanying acute parietal appendicitis suggests the importance of a secretory mechanism in addition to complete luminal obstruction for the production of acute experimental appendicitis.

OBSTRUCTION OF VERMIFORM CECAL APPENDAGE IN CHIMPANZEES

Three chimpanzees were used in these experiments. In the first the experiment was terminated after ten hours by death due to a mucous plug in the trachea. Extensive tuberculosis of the lungs and peritoneum was observed at autopsy. The intraluminal secretory tension developed to a pressure of 42 cm. of water during the ten hour period. Microscopic examination revealed diffuse leukocytic invasion of all the walls. In the second animal the highest intraluminal appendical pressure was 76 cm. of water, attained in twenty hours. There was no further increase for eight and a half hours, when a gradual decrease in pressure followed. The experiment was terminated thirty-three hours after the induction of obstruction. Examination revealed a rupture of the appendical wall in the proximal portion of the appendix, which was beneath the skin. Sections showed mucosal appendicitis, group A, grade 3. The third chimpanzee built up an intraluminal pressure of 106 cm. of water in thirty-three hours and maintained it for three hours, when rupture occurred (fig. 5). Microscopically, a diffuse polymorphonuclear leukocytic invasion was observed in the walls of the 3 appendixes removed ten, thirty-three and forty-two hours after obstruction.

OBSTRUCTION OF EXTERIORIZED APPENDIX IN MAN

Forty-two appendicostomy studies have been made since February 1936 (table 5). The earlier observations were made on the unobstructed exteriorized appendix. A connection was made to a manometric recording system, and kymographic tracings were obtained. During the last two years similar observa-

12. Bizzozero, G.: Centralbl. f. d. med. Wchnschr. **23**:801, 1885.

13. Ghon, A., and Namba, K.: Beitr. z. path. Anat. u. z. allg. Path. **52**:130, 1912.

14. Wangensteen, O. H., and Dennis, C.: Ann. Surg. **110**:629, 1939.

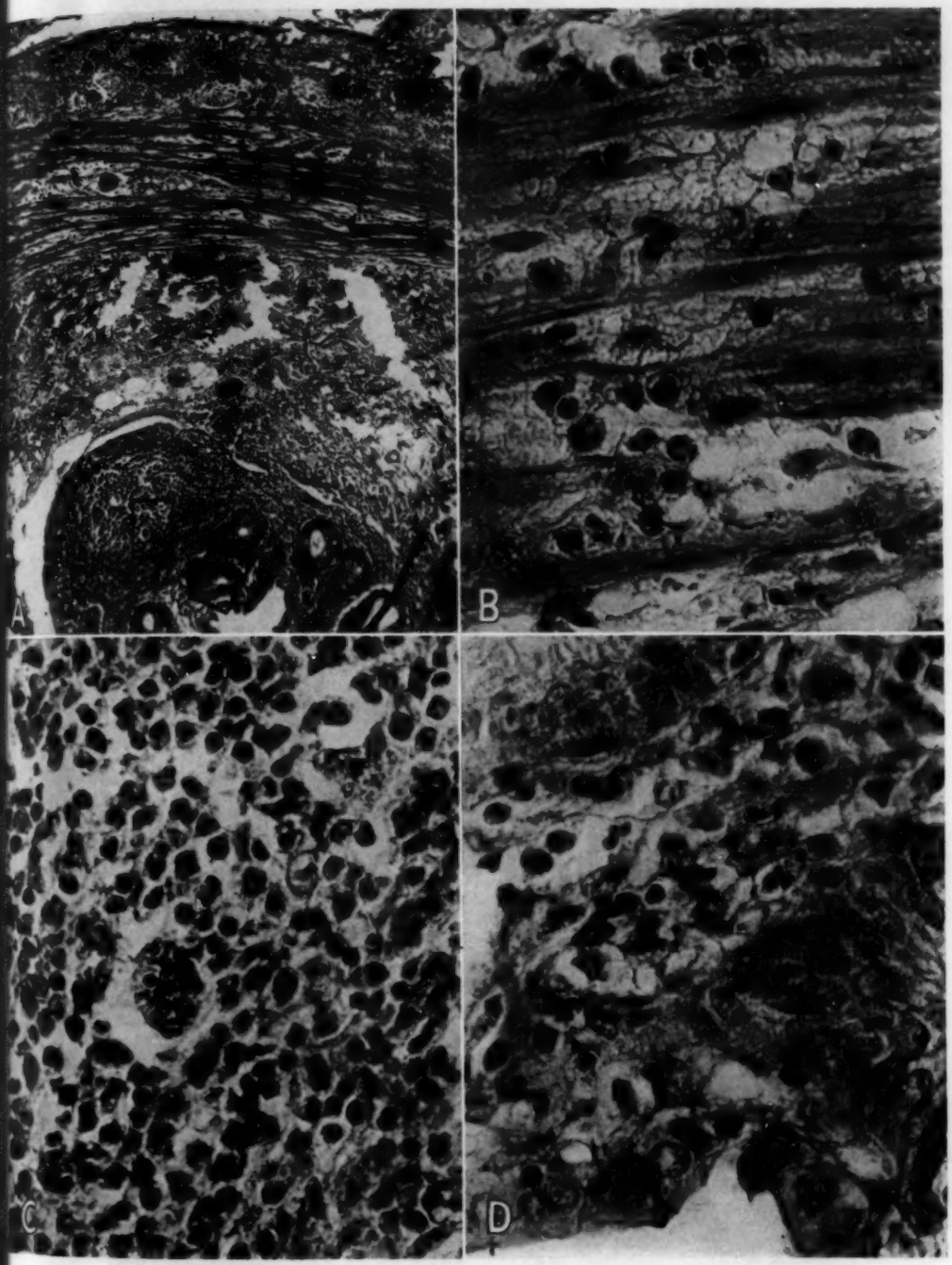

Fig. 5.—Chimpanzee. Photomicrographs of the microscopic changes found in the appendical wall incidental to obstruction of the appendical lumen, associated with an intraluminal pressure of 106 cm. of water and perforation. *A*, acute inflammatory changes throughout the appendical wall; × 55. *B*, degeneration of muscle fibers with invasion of the muscularis by leukocytes; × 504. *C*, lymphatic nodule containing polyblasts with ingested cellular debris. *D*, polymorphonuclear leukocytes in the lamina propria of the mucosa. Diffuse appendicitis, grade 1.

tions have been made on obstructed, exteriorized appendixes,[14] a fine plain catgut ligature having been placed at the base of the appendix at the time of operation. After a temporary period of obstruction the lumen usually opened spontaneously, and the appendix exteriorized beyond the skin was amputated; granulations grew over the appendical stoma at the skin and complete healing occurred.

The usual procedure after the acute period of appendical obstruction was to drain the appendical lumen by incannulation with a small glass cannula, and some time later to perform an extraperitoneal appendectomy. However, in 10 cases, after appendicostomy, appendectomy was performed at the end of only a brief interval following the period of acute obstruction. Blocks of appendical tissue were taken from the tip of the appendix at the time of the incannulation for comparison with blocks taken at the time of final excision of the exteriorized

TABLE 5.—*Results Attending Obstruction and Incannulation of the Exteriorized Cecal Appendage of Man*

Specimen	Time of Acute Obstruction	Pressure, Cm.	Procedure	Diagnosis
1	21.0 hr.	42.0	Appendectomy at end of 42.0 hr.	Diffuse appendicitis, grade 1
2	26.0 hr.	0.0	Appendectomy at end of 48.0 hr.	Diffuse appendicitis, grade 1
3	19.0 hr.	90.0	Appendectomy at end of 48.0 hr.	Mucosal appendicitis, group A, grade 3
4	22.0 hr.	92.0	Appendectomy at end of 70.0 hr.	Mucosal appendicitis, group A, grade 3
5	24.0 hr.	126.0	Appendectomy at end of 72.0 hr.	Mucosal appendicitis, group A, grade 3
6	15.0 hr.	125.0	Appendectomy at end of 6.5 days	Mucosal appendicitis, group A, grade 3
7	49.0 hr.	114.0	Appendectomy at end of 6.5 days	Mucosal appendicitis, group A, grade 3
8	24.0 hr.	8.0	Appendectomy at end of 13.0 days	Healing appendicitis, with obliteration of the lumen
9	7.0 hr.	32.0	Appendectomy at end of 2 mo.	Healing appendicitis
10	12.0 days	....	Control: appendectomy at end of 12.0 days; appendicostomy incannulated; not obstructed	Diffuse appendicitis, grade 2

appendix. In twelve of the twenty-two experiments the sections taken were unsatisfactory for study because of the length of time the appendix was exteriorized.

Sections from the obstructed, exteriorized appendixes revealed that the histologic change represented three of the following four types of inflammatory reactions found in acute spontaneous appendicitis.

1. In 5 appendixes with obstruction and appendicostomy, and secretory pressures over 90 cm., the mucosa was heavily infiltrated with leukocytes (mucosal appendicitis, group A) which appeared not unlike catarrhal (*Primärinfekt*) appendicitis.

2. A diffuse inflammatory process involving all the walls (diffuse, phlegmonous, ulcerative, gangrenous) was noted in 2 appendixes with obstruction and appendicostomy and 1 appendix with appendicostomy but unobstructed. The latter had harbored a soft rubber catheter in the lumen for twelve days; on sections the mucosa was intact, with a few leukocytes in the lamina propria, the external layers were heavily infiltrated with leukocytes, and areas of fibrosis were noted through-

out. In another (table 5, no. 2) no pressure was observed, and sections showed an absence of the mucosal layer. The reaction was characteristically a diffuse infiltration of neutrophilic leukocytes in all the layers.

3. A subserosal perivascular leukocytic invasion was not encountered, as all the reactions were decidedly more severe.

TABLE 6.—*Summary of the Histologic Appendical Reactions Attending the Experimental Procedures* *

	Histologic Diagnosis															
		Normal Serosal Appendicitis		Mucosal Appendicitis							Diffuse Appendicitis					
				Group A			Group B									
	Normal	Grade 1	Grade 2	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Healing Appendicitis	No Sections	Total
1. Control series	4	..	3	..	..	1	..	..	..	..	..	1	..	..	9
2. Unwashed, obstructed	..	2	..	..	4	..	..	..	8	..	6	3	3	..	26
3. Washed, obstructed	..	..	..	..	..	..	..	..	..	..	1	2	2	..	5
4. Unwashed, proximally obstructed series	..	10	..	..	..	..	..	..	..	..	..	1	..	..	11
5. Washed, incannulated	..	..	1	..	..	..	2	1	..	4	2	2	..	..	12
6. Obstruction, drugs †	..	1	..	..	..	..	..	..	1	..	1	..	..	..	3
7. Obstruction, croton oil series	..	..	1	..	2	..	..	4	..	1	3	..	..	..	11
8. Obstruction, magnesium sulfate, castor oil	..	1	..	..	..	1	..	1	1	2	..	..	..	..	6
9. Obstruction, hypertonic saline series	..	5	2	..	..	3	..	2	2	2	2	..	..	..	18
10. Unwashed, incannulated, obstructed series	..	2	1	..	..	..	..	1	..	1	..	..	..	..	5
11. Traumatized, obstructed	..	..	..	..	1	1	..	..	..	..	..	1	3	..	6
12. Incannulated, curetted, obstructed series	..	..	..	..	..	..	..	..	..	..	4	2	..	..	6
13. Obstructed, constant pressure series	..	6	2	..	..	..	2	..	3	2	3	2	..	..	20
14. Intraperitoneal fluid collection series	..	5	..	..	1	..	..	..	..	..	2	..	2	..	10
15. Obstruction appendicostomy	..	..	..	..	..	..	..	..	..	..	1	..	..	4	4	9
16. Obstruction, circulation compromised	..	..	..	..	..	..	1	2	..	2	..	..	1	..	6
17. Chimpanzee: appendix obstructed and exteriorized	..	..	..	..	..	2	..	..	..	..	1	..	..	..	3
18. Man: appendix obstructed and exteriorized	..	..	..	..	..	5	..	..	..	..	2	1	2	..	10

* Items 1 to 16 inclusive refer to the rabbit; item 17 concern the chimpanzee, and item 18, man.

† Pilocarpine, epinephrine and pitressin were administered during luminal obstruction.

Healing phases of appendicitis, exhibiting granulation tissue reaction and luminal obliteration of varying grades (displacement of lymph follicles into the muscular and subserous coats, invasion and replacement of the appendical wall with fat and mucocele formation) is exemplified by sections (table 5, no. 9) which revealed healing by granulation tissue and fibrosis, and healing appendicitis (table 5, no. 8) with obliteration of the lumen.

From the studies which have been made on the histologic response attending artificial obstruction of the vermiform cecal appendage of man,

the chimpanzee and the rabbit, it appears that all the observed and recognized varieties were produced experimentally by incannulation and induced obstruction of the appendical lumen.

COMMENTS

Rabbit.—The pathologic changes characteristic of acute spontaneous appendicitis appear to a varying degree in artificially obstructed and nonobstructed cecal appendages. In the latter the reaction was serositis. The factor of mechanical trauma produced a serosal inflammatory reaction, which occasionally involved the muscularis layer of the appendical wall. In the nongangrenous tissues the area of greatest inflammatory change was usually near the site of obstruction. In gangrenous perforated areas the inflammatory reaction was characteristically suppurative.

The results attending ligature obstruction of the rabbit's cecal appendage in the early stages (four to six hours) were frequently found to be associated with minimal histologic changes, primarily of a histogenous type. Later stages (eight to ten hours) were characterized by varying degrees of hematogenous polymorphonuclear eosinophil leukocytic infiltration (rabbit heterophil), and frequently gangrenous changes were found. Early functional changes of the appendage were not promptly represented by gross or microscopic changes.

This apparent latent period of inflammatory reaction may find its clinical counterpart in the surgeon's experience of performing an appendectomy only to have the pathologic report fail to confirm his clinical diagnosis. Cutler [15] has described the ingestion of leukocytes by large phagocytic cells in the lymphatic nodule as evidence of early mild acute appendicitis. Structural changes in the appendical wall, such as increased interstitial tension and changes in appendical secretory activity, associated with mild grades of temporary obstruction, not manifest by organic change, may find clinical expression as mild attacks of pain.

The duration of induced obstruction of the appendical lumen in the rabbit and the magnitude of the intraluminal pressure during the period of obstruction were not observed to result in acute inflammatory changes the degree of which could be anticipated by the duration of obstruction or the pressure sustained. Frequently a minimal reaction was observed when the pressure was low, and a high pressure during a short interval was accompanied by acute changes and often by gangrene or rupture.

A period of obstruction followed by release of the obstruction was attended by traumatic serositis. Obstruction when accompanied by

15. Cutler, O. I.: Arch. Surg. **31**:729, 1935.

trauma to the mucosa was invariably associated with marked inflammatory changes. The site of the obstruction apparently does not influence the extent of the inflammatory reaction or the complication of rupture, which usually was some distance removed from the area of artificial obstruction. Rupture attended somewhat more than 40 per cent of the acute obstructions of appendages, with local or generalized peritonitis. Obstruction of approximately ten hours' duration resulted in perforation in 75 per cent of the cases. In the absence of obstruction two uncontrollable factors, trauma and infection, were never attended by rupture, and the reaction was usually a serosal lesion.

In the cecal appendages of 2 rabbits appendicoliths found at the time of obstruction were allowed to remain undisturbed in the appendical lumens, and following a period of obstruction the masses were found to have been dissolved by the secreted fluid.

The degree of granulocytic invasion in the rabbit's appendical tissue was generally less than that found in other tissues (chimpanzee and man). A greater macrophagic response took place in the appendical tissues of the rabbit.

Gibbon.—One of the 2 gibbons had an inflammatory exudate in the lumen of the vermiform cecal appendage. It is likely that such a finding represents a greater degree of involvement than that represented by the changes found in the appendical wall, and it may be explained by the considerable manipulation accompanying the determination of the luminal volume of the appendix, tests of luminal resistance and faradic stimulation of the appendical wall prior to the onset of induced obstruction.

In the two experiments the intraluminal appendical pressure developed to 18 and 19 cm. of water; however, in neither instance was this maximal pressure maintained. In the instance of induced obstruction of the cecal appendage of the rabbit, sustained intraluminal pressure of low magnitude over a long period of time was required to produce suppurative histologic changes in the appendical wall. In the absence of more convincing evidence it appears that sustained secretory pressure is an essential factor for the production of leukocytic invasion of the obstructed and incannulated appendix of the gibbon.

Chimpanzee.—Weinberg [16] found evidence of acute suppurative appendicitis in 10 of 61 chimpanzees dying in captivity. In addition to the structural similarity between the chimpanzee's appendix and the

16. Weinberg, quoted by Wangensteen, O. H., and Bowers, W. F.: Arch. Surg. **34**:496, 1937.

human appendix, there has been shown a physiologic similarity under certain experimental conditions.[17] The chimpanzee's appendix, like that of man, is capable, after induced obstruction, of producing an elevation in intraluminal pressure (106 cm. of water). The resulting inflammatory response defies histologic distinction from that observed in a series of exteriorized obstructed human appendixes.

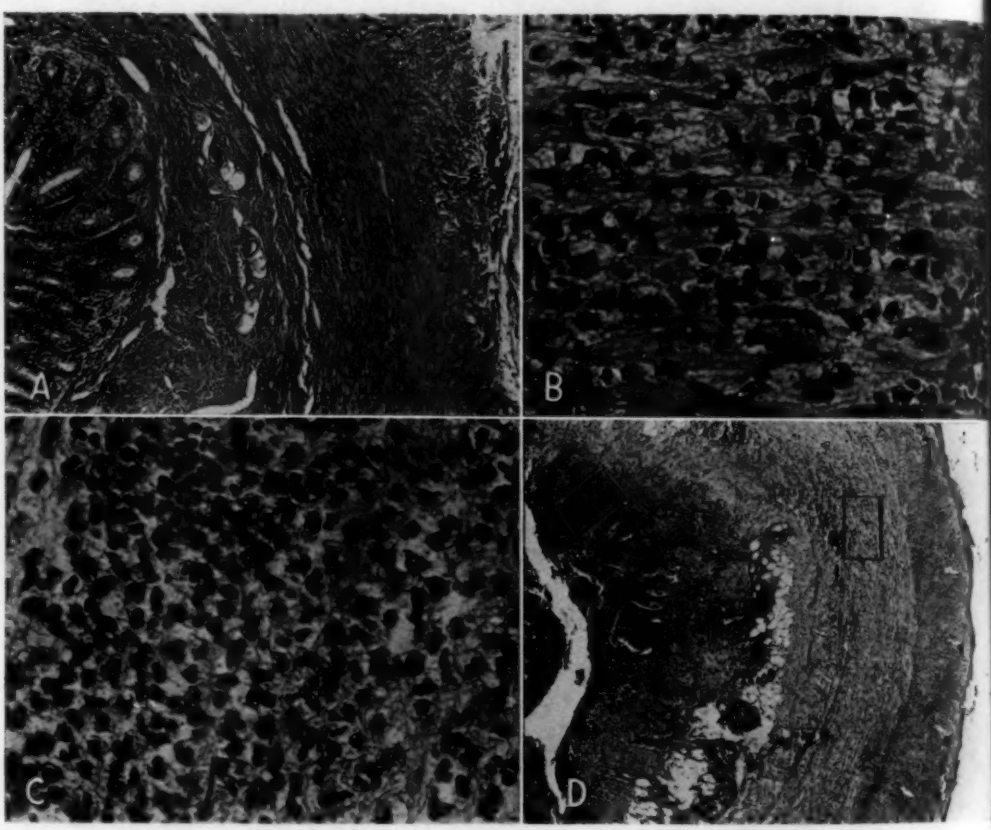

Fig. 6.—Man. Photomicrographs depicting the histologic reaction attending obstruction of the exteriorized appendix of men (table 7). Appendix in case 7, table 9, obstructed for forty-nine hours; intraluminal pressure, 114 cm. of water. *A*, control section from the tip of the appendix at the time of incannulation; × 44. *B*, small area shown in *D*, demonstrating the presence of polymorphonuclear leukocytes in the muscularis; × 400. *C*, squared area in *D*, showing invasion of leukocytes in the mucosal layer of the appendix; × 400. *D*, acute inflammatory changes in the mucosa, muscularis and serosa; × 44. Mucosal appendicitis, group A, grade 3.

17. Dennis, C.; Buirge, R. E., and Wangensteen, O. H.: Surgery **7**:372, 1940.

The chimpanzee's obstructed appendix presented a pathologic picture similar to that found in the obstructed, exteriorized appendix in man.

Nature of Luminal Exudate Found in Experimental and Spontaneous Appendicitis in Man.—The obstructed, exteriorized appendix of man

TABLE 7.—*Differential Cell Counts of Luminal Exudate in Seven Human Appendixes Without Evidence of Inflammatory Cellular Exudate in the Appendical Wall*

			Differential Cell Count				
Patient	Sex	Age	Polymorphonuclear Neutrophils	Polymorphonuclear Eosinophils	Lymphocytes	Smudge Cells	Histologic Diagnosis
1	F	13	12	0	88	0	Inactive appendix
2	F	18	0	0	75	25	Inactive appendix
3	F	30	9	0	91	0	Inactive appendix
4	F	30	4	0	95	1	Inactive appendix
5	F	42	0	0	95	5	Inactive appendix
6	M	21	0	0	96	4	Inactive appendix
7	M	25	0	2	93	5	Inactive appendix
Average			4		90	6	

TABLE 8.—*Differential Cell Counts of Luminal Exudate in Appendixes of Patients with Spontaneous Appendicitis*

				Differential Cell Count				
Patient	Sex	Age	Onset to Time of Operation, Hr.	Polymorphonuclear Neutrophils	Lymphocytes	Monocytes	Smudge Cells	Histologic Diagnosis
1	F	16	12	88	10	..	2	Diffuse appendicitis
2	F	35	12	78	22	..	0	Diffuse appendicitis
3	F	17	14	96	4	..	0	Diffuse appendicitis
4	F	23	20	95	5	..	0	Diffuse appendicitis
5	F	40	21	90	9	..	1	Diffuse appendicitis
6	M	27	8	76	16	4	4	Diffuse appendicitis
7	M	7	10	80	12	4	4	Diffuse appendicitis
8	M	26	11	78	19	..	3	Diffuse appendicitis
9	M	28	12	92	7	..	1	Diffuse appendicitis
10	M	34	12	84	8	..	8	Mucosal appendicitis
11	M	56	12	85	15	..	..	Diffuse appendicitis
12	M	15	16	80	12	..	8	Diffuse appendicitis
13	M	13	17	91	6	..	3	Diffuse appendicitis
Average				86	11		3	

presented pathologic changes, the detailed cytologic nature of which corresponded to that of spontaneous appendicitis. Further correlation between spontaneous and experimental appendicitis is offered by a cytologic study of the luminal exudate found in such appendixes. Differ-

ential cell counts were made in a series of spontaneously affected appendixes and also in a group of exteriorized obstructed human appendixes.

Counts were made on luminal exudate in sections obtained from blocks of appendixes stained with hematoxylin and eosin.

In a series of 26 appendixes from patients with complete diagnostic surveys and free from any known infection 7 selected appendixes were studied. A differential cell count made of the luminal exudate revealed a predominantly large number of lymphocytes (table 7) (90 per cent). In a summary of 19 hospital cases with complete history and findings of acute appendicitis and with diffuse inflammatory changes in the

TABLE 9.—*Cell Counts of Exudate in Obstructed Appendical Lumen of Exteriorized Appendixes*

	Differential Cell Count			
Specimen	Polymorphonuclear Neutrophils	Lymphocytes	Smudge Cells	Histologic Diagnosis
1	78	22	..	Diffuse appendicitis, grade 1
2	84	4	12	Diffuse appendicitis, grade 1
3	90	4	6	Mucosal appendicitis, group A, grade 3
4	88	8	4	Mucosal appendicitis, group A, grade 3
5	87	5	8	Mucosal appendicitis, group A, grade 3
6	Lumen empty			Mucosal appendicitis, graup A, grade 3
7	68	24	8	Mucosal appendicitis, group A, grade 3
8	Lumen obliterated			Healing appendicitis, obliteration lumen
9	Incomplete cross section			Healing appendicitis
10	76	20	4	Diffuse appendicitis, grade 2
Average	82	12	7	

appendical wall, 13 in which luminal exudates were found showed an average polymorphonuclear count of 86 of every 100 cells counted (table 8). Similarly the luminal exudate in the group of 6 obstructed, exteriorized appendixes had an average polymorphonuclear leukocyte count of 82 of every 100 cells counted (table 9). Thus it may be said that the same type of inflammatory cellular exudate is present in the luminal content of the human obstructed, exteriorized appendix as is found in the lumens of appendixes removed from patients with acute spontaneous appendicitis.

Colicky pain not unlike that of patients with spontaneous appendicitis has been reproduced in a patient with an obstructed, exteriorized appendix by temporarily blocking the egress of appendical fluid. The histologic changes incidental to such functional alteration are of primary concern in the pathologic diagnosis of early appendicitis.

SUMMARY

Acute inflammatory, obstructive, gangrenous and ruptured parietal appendicitis have been produced experimentally in the rabbit, chimpanzee and man.

Bacteria were found to be present in the lymphatic follicular zone of the normal and of the obstructed cecal appendage of the rabbit.

The release of appendical obstruction resulted in prompt repair of injured tissues.

Early appendicular obstruction was attended by minimal histologic inflammatory changes.

Differential cell counts on exudate in appendical lumens in experimental and in spontaneous appendicitis were found comparable.

The histologic picture of diffuse appendicitis in man has been reproduced by induced obstruction in the exteriorized vermiform appendix.

Luminal obstruction in an appendix with an active secretory function would appear to be the dominant factor in provoking appendicitis.

TISSUE CULTURE AS A DIAGNOSTIC AID IN THE IDENTIFICATION OF ATYPICAL TUMORS

MACHTELD E. SANO, M.D.
AND
LAWRENCE W. SMITH, M.D.
PHILADELPHIA

Not infrequently the pathologist is confronted with a problem of difficult histogenetic diagnosis in the case of certain tumors. It is not sufficient that he should recognize only their malignant character. The tumor requires classification so that its natural history may be understood and the subsequent recognition of a similar tumor made possible. Not rarely the prognosis depends on such accurate differentiation. At times even the autopsy may not solve the problem, and the tumor goes down in the records as unclassified. We suggest the use of tissue culture as an accessory diagnostic aid in such doubtful cases. This procedure confirmed our tentative conclusions in 2 cases of this nature. These we shall present in the hope that this suggestion may be of help to others confronted by such problems.

REPORT OF CASES

CASE. 1.—A 36 year old white married woman was admitted because of multiple small subcutaneous nodules distributed rather generally over the body. They were nonpigmented and freely movable. Five years previously the patient had a pigmented mole removed, by her family physician, from the right leg just below the knee. This recurred rather promptly in the scar at the site of the original tumor, and was again removed by electrocoagulation and wide excision. The pathologic diagnosis given at that time was "benign nevus, pigmented." One year before the present admission the patient consulted another physician because of a small nodule in Scarpa's triangle on the right. On the advice of the physician she received intensive preoperative roentgen treatment. The lesion was then removed surgically and at that time was diagnosed clincally as metastatic melanoma. The tumor again recurred promptly, and she was given further roentgen treatment locally but with no further regression of the lesion.

Because of the complete absence of pigmentation of the lesions on this admission, a biopsy was made on tissue from one of the cutaneous nodules for the purpose of establishing a diagnosis. Histologic examination revealed an extremely atypical, rather spindle cell tumor which contained no pigment. A tentative diagnosis of amelanotic melanoma malignum was made, largely on the basis of the history rather than on the histologic appearance of the tumor. A portion of the biopsy specimen was utilized for tissue culture.

From the Department of Pathology, Temple University School of Medicine, and the Temple University Hospital Tumor Clinic.

The patient died about three weeks after admission. Autopsy revealed widespread visceral metastases involving the heart, lungs, liver, pancreas and ovaries, as well as being distributed throughout the mesenteric and subcutaneous tissues.

Histologic study of many of these metastatic tumor nodules showed a similar picture in all. The cells were rather regularly arranged in alveolar fashion, separated by narrow bands of connective tissue stroma. They were uniform in size and in staining qualities, although there was some tendency toward nuclear hyperchromatism. No pigment was found either macroscopically or microscopically in any section. Because of the curious histologic character of the tumor, a positive diagnosis was difficult. In the ovary one could almost imagine seeing a transition from the ovarian stroma to tumor cells, but in other tissues, such as the pancreas, there also seemed to be a gradual transition from the specific organ tissue to

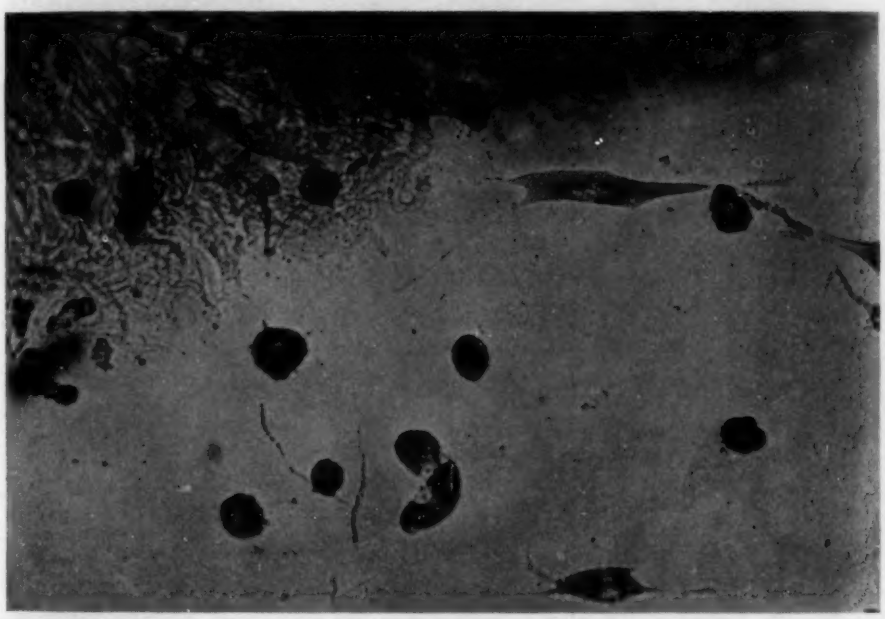

Fig. 1.—Note the deeply pigmented tumor cells migrating from the mother colony. Isolated pigment granules can be seen in the interstices of the culture.

tumor tissue. A dopa reaction could not be obtained at the time, using fresh tissue, because of a lack of the necessary reagents, and when performed subsequently, was unsatisfactory.

The tissue which was removed from the biopsy specimen for culture was placed, immediately after removal, in the refrigerator at a temperature ranging from 0.5 to 1 C. Forty-eight hours later it was transplanted to Lewis tubes and to our cover glass containers, which readily permit microscopic examination under high power.[1] (The exposure of tumor cells to low temperatures is part of a more extensive experiment relating to the effect of low temperature on tumor cells.[2])

1. Sano, M., and Smith, L. W.: Proc. Soc. Exper. Biol. & Med. **28**:282, 1930.

2. Smith, L. W., and Fay, T.: J. A. M. A. **113**:653, 1939.

The usual medium for tissue culture, containing calf embryo extract, chicken plasma and Tyrode's solution, was used. About fourteen days after the initial inoculation, migration of a few fibroblasts and clasmatocytes was observed. On the eighteenth day a few large round cells began to appear. These contained a variable number of deep-staining pigment granules, rather evenly distributed throughout the cytoplasm. Certain of these cells showed the development of small, short pseudopodia. Because of the inadequacy of these structures, migration of these cells was slow (fig. 1). In addition to the pigment granules filling the large cells (some of these cells were so deeply pigmented as to appear almost solid black), occasional granules of pigment could be seen lying free in the medium. The mother colony likewise showed irregular patches of pigmentation grossly.

Cultures from a reticulocell sarcoma which were grown under the same conditions and at the same time showed no pigment production. The Roffo test was positive and the test for iron negative. On the basis of these features we believe that we are justified in establishing the diagnosis of this tumor as a malignant melanoma showing amelanotic features clinically. Under the artificial conditions of tissue culture, with the provision of a medium which apparently contained the necessary oxidizing enzyme, the melanogen became converted into visible melanin. The appearance of pigmentation during the cultivation of the tumor in vitro might also be explained on the basis of changed metabolic activity, as shown by Masson.[3]

The use of tissue culture for the establishment of the diagnosis of melanoma in similar cases of indefinite amelanotic tumors is suggested.

Case 2.—An 18 month old boy was admitted with the following history: He had had a cold four weeks before admission. This was followed, a week after the onset, by a marked swelling of the supraorbital tissues on the right. This was accompanied by swelling of both submaxillary glands. It was thought that he had mumps. However, the swelling progressed, and the child was brought to the hospital, where a biopsy of one of the regional cervical lymph nodes, which likewise by this time showed enlargement, was made. Routine sections were cut, and a tentative diagnosis of atypical lymphosarcoma was made. The histologic appearance was so unusual, however, that there was considerable uncertainty as to the accuracy of the diagnosis. The patient was treated intensively by irradiation but without apparent effect on the continued growth of the tumor.

Because of our experience in the identification of the tumor in case 1, a similar procedure was followed in this case. This, again, was part of the larger research program of studying the cell changes associated with "hibernation." The tumor tissue was transplanted into Lewis tubes and our own modified tissue culture apparatus.

Within forty-eight hours there was a fairly profuse growth of fibroblasts. Beginning about ninety-six hours after inoculation of the medium, a few large cells migrated far away from the mother culture. These tended to clump together and continued to proliferate independently until they produced a large island made up entirely of these cells. They presented the usual morphologic picture which is found in tissue cultures of the reticulocell type of lymphosarcoma. They were

3. Masson, P.: Ann. d'anat. path. **3**:417 and 657, 1926.

large rounded cells with uniform nuclei, which tended to be spherical and had a rather characteristic distribution of the chromatin throughout. Here and there a tendency toward the formation of reticulum was observed (fig. 2).

Cultures from this tumor have been maintained now for over six months, notwithstanding several weeks of far from ideal conditions, owing to our inability to secure a supply of fresh embryonic extract. During this period the cells lost their reticular processes, shrank and at times appeared almost crenated. In stained preparations both cytoplasmic and nuclear changes were so marked as to suggest an actually irreversible state. However, after remaining dormant in this condition for nearly six weeks, with the renewal of suitable medium they again began to migrate and proliferate afresh.

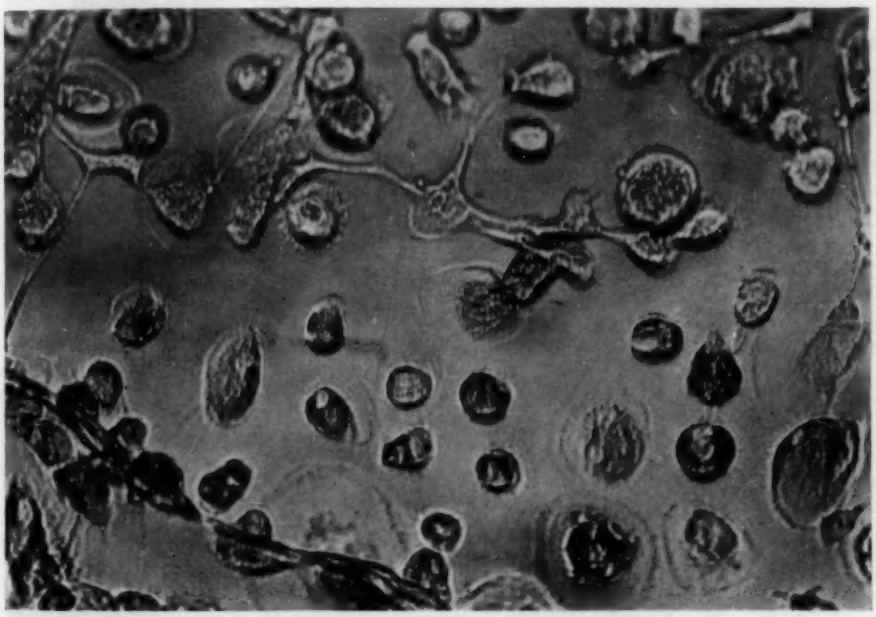

Fig. 2.—The tumor cells in this case are seen as of varying size, tending to be spherical, with large nuclei. Observe the tendency toward the formation of reticulum.

In connection with these biopsies we have likewise found the method of value in determining the viability of tumor tissue which has been treated by local or general refrigeration. By the usual histologic criteria of biopsy sections it is sometimes difficult to decide whether there are any viable tumor cells, because of the extensive regressive changes present. However, when such apparently necrotic tumor tissue was inoculated into a suitable medium, cell growth occurred after a brief period of delay. For example, in another case of malignant tumor of lymphoid origin, as is frequently the case, the fibroblasts were the first cells to appear, but these were followed within the next few days by

a growth of typical tumor lymphocytes. The latter migrated freely and could be readily recognized as immature forms by the "hand mirror" form described by Rich, Wintrobe and Lewis.[4]

As one's familiarity with the appearance of the various cell types in tissue culture increases, the utilization of this method as a diagnostic aid in the classification of such debatable tumors, we believe, will assume an ever increasing position of importance.

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4. Rich, A. R.; Wintrobe, M. M., and Lewis, M. R.: Bull. Johns Hopkins Hosp. **65**:291, 1939.

RELATIONSHIP OF BODY WEIGHT TO CANCER INCIDENCE

ALBERT TANNENBAUM, M.D.
CHICAGO

Cancer is the result of many extrinsic and intrinsic factors. Some of these are well established, while others are little more than hypothetic. The possibility that body weight is one of these factors has been indicated in recently reported animal experimentation. The results of this work led me to review the available studies on human insurance statistics dealing with cancer mortality and body weight. The studies on animal and human subjects are reported and evaluated.

EXPERIMENTAL WORK ON ANIMALS

In a recent publication [1] I reported the effects of a weight-restricting diet on the inception of tumors in mice. Tumors developed in fewer mice in the underfed groups than in the corresponding control, full fed groups. Furthermore, the tumors in the underfed mice appeared at a later time. These results were obtained with all strains of mice and all types of tumors utilized: spontaneous tumors of breast and lung, and carcinomas and sarcomas induced by cancerigenic agents.

The control, full fed animals were fed daily 4.5 Gm. of an adequate basic diet and consumed from 3.8 to 4.2 Gm. per animal per day. The underfed animals were given the identical diet but in amounts ranging from one-third to one-half that fed the control animals. The exact amount was such as to keep the individual mice in the underfed group at a weight of 18 to 20 Gm., in comparison with a weight of 28 to 40 Gm. for the control animals.

The underfed mice appeared perfectly healthy, were active and sleek, and, in general, lived longer than the control mice. There was no evidence of vitamin or mineral deficiency.

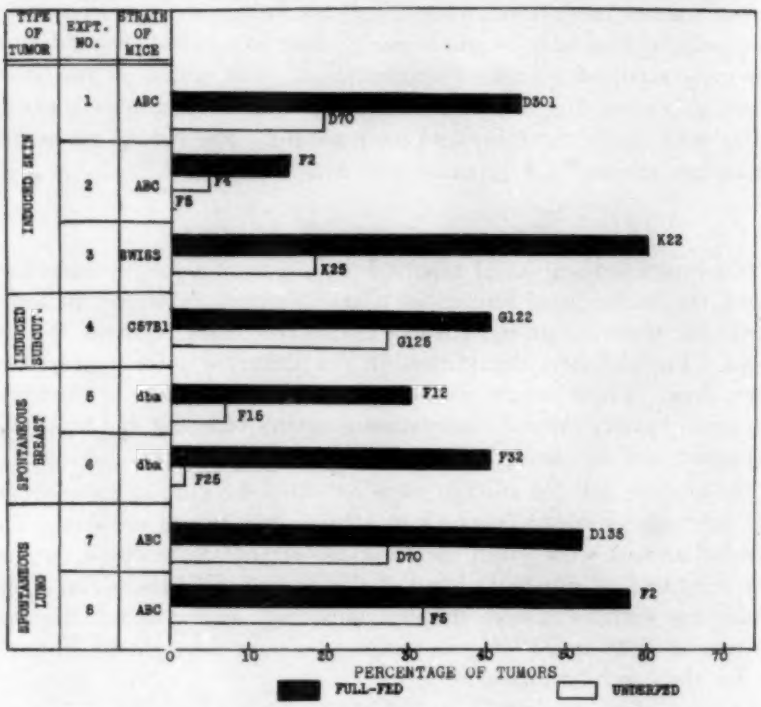
In the accompanying chart the percentage of tumors arising in the underfed group (white bar) of each experiment is compared with the percentage of tumors arising in the corresponding full fed control group (black bar). The types of tumors and the strains of mice are also listed in the chart. The complete protocols are reported in the original publication.

From the Tumor Research Laboratory (supported by the Lebold Research Fund), Michael Reese Hospital.

1. Tannenbaum, A.: Am. J. Cancer **38**:335, 1940.

It can be seen that the experiments differ in the degree of inhibition of tumor formation but that there is no question of the nature of this effect: Fewer tumors develop in underfed mice.

This relationship might also be quantitative. For example, in experiment 2 there were three groups: F2, full diet, mean weight 36 Gm.; F4, moderately restricted diet, mean weight 25 Gm., and F5, greatly restricted diet, mean weight 20 Gm. At these three weight levels, 36, 25 and 20 Gm., under the same experimental conditions of inducing



Effects of underfeeding on the initiation of induced and spontaneous tumors in mice. (From Tannenbaum.[1])

tumors, there were formed, respectively, 15, 5 and 0 per cent tumors. The relationship may not be continuous or gradual but dependent on relatively large differences in weight.

It should also be noted that McCay and associates,[2] in a study on rats retarded by restricted food intake, reported, as an incidental finding, limited evidence indicating a lower incidence of tumors in the retarded animals.

2. McCay, C. M.; Ellis, G. H.; Barnes, L. L.; Smith, C. A. H., and Sperling, G.: J. Nutrition **18**:15, 1939.

INSURANCE STATISTICS

For many years life insurance companies have been studying the relationship of various factors to the principal causes of death. Through an understanding of these relationships they can adjust their premium rates; at the same time, valuable statistics on man are made available. Some of these statistical studies throw light on the relationship of body weight to cancer mortality. Although the statistics refer to cancer mortality, one is practically dealing with cancer incidence, since cancer mortality corresponds in general to cancer incidence. These analyses have indicated that overweight persons past middle age are more likely to die of cancer than are persons of average weight.

In reviewing the results of an analysis of insurance statistics one must recognize the fact that the material itself presents many complicating factors. The composition of the groups must be affected by the extended period over which the study is made, the broad area from which policyholders are drawn, the varying ages, the divergent dietary habits, the race and the hereditary characteristics of build, medical selection and the grouping of various types of cancer. Also, the weight of the subject is taken only at the time the policy is issued, and many years may elapse between the original weighing and the death from cancer. During this interval the weight may change. Moreover, the diagnosis of cancer is taken from the death certificate, and it is well known that a considerable proportion of such diagnoses are not based on biopsies or autopsies. The statistical investigators for insurance companies have accounted for these factors by various technics and have effected reports that are in general valid and of great value. The exact methods of analysis are complex, and no attempt will be made to discuss them in this paper. The various studies are discussed in the order in which they were published.

"Medico-Actuarial Mortality Investigation." [3]—In 1913 a comprehensive analysis of the principal causes of death was reported by a joint committee of the Association of Life Insurance Medical Directors and the Actuarial Society of America. The report dealt with 774,672 policies (1885-1908) on men whose ages were from 20 to 62, inclusive, and whose heights ranged from 5 feet 3 inches to 6 feet 2 inches (160 to 188 cm.). The figures for age, weight and height were those of the policyholder at the time his first policy was issued.

The policyholders were divided into three groups: overweight, those 50 pounds (23 Kg.) or more over the average weight; standard, those less than 50 pounds overweight and not more than 25 pounds (11 Kg.)

3. Medico-Actuarial Mortality Investigation, Actuarial Society of America and Association of Life Insurance Directors, New York, Spectator Company, 1913, vol. 2.

underweight; and underweight, those who were 25 pounds or more under the average weight. The mortality rate is given as "deaths per 100,000 exposed to risk."

For men accepted for insurance between the ages of 30 and 44, the subsequent mortality rates for cancer of the overweight, standard and underweight groups were 37, 32 and 24, respectively; for the age group of 45 years and over, the figures were 156, 144 and 120, respectively. This study suggests that with increasing body weight there is an increase of cancer mortality. The actual differences and gradation of mortality rates are striking!

Union Central Life Insurance Company Records.—Dublin [4] made an analysis of cancer mortality according to weight among men who had taken out policies at 45 years of age and over and had subsequently died of cancer. He utilized approximately 192,000 records (1887-1921) of the Union Central Life Insurance Company. In this study, also, the policyholders were classified according to weights at entry. The analysis resulted in the following distribution of cancer mortality with regard to weight.

Weight at Issue of Policy	Cancer Mortality per Hundred Thousand
25 per cent or more overweight	143
15 to 25 per cent overweight	138
5 to 15 per cent overweight	121
Normal weight	111
5 to 15 per cent underweight	114
15 to 50 per cent underweight	95

This study reveals a gradation in mortality rates sufficiently consistent to indicate that cancer incidence increases with increasing weight.

Death Claims of Ordinary Department of the Metropolitan Life Insurance Company for 1927.—Dublin [4a] classified policyholders dying from cancer, on the one hand, and from accidents, on the other, according to their weight at the time their policies were issued. He considered the accidental death group comparable in weight distribution to the general population. He found that for ages over 45 the relative number of those excessively overweight among persons dying of cancer was nearly 25 per cent greater than among those dying of accidents.

An analysis by age groups revealed no essential differences between the weight distributions of the cancer and accident groups at ages under 45. However, in the age group of 45 to 64, 55 per cent of those dying from cancer were average weight or more, whereas only 48 per cent of those dying from accidents were of average weight or more. For ages

4. (*a*) Dublin, L. I.: Proc. A. Life Insur. M. Dir. America **15**:402, 1929; (*b*) Bull. New York Acad. Med. **8**:687, 1932. (*c*) Jackson, D.: Texas State J. Med. **24**:622, 1929.

of 65 and over, those of average weight or more comprised 51 per cent of the cancer death group, in comparison with 43 per cent of the accidental death group.

If the accidental death group is an adequate representation of the general population, the results indicate that a comparatively high percentage of those dying from cancer are of average weight or more.

"Medical Impairment Study."—In 1932 there was published a supplement to the "Medical Impairment Study," entitled "Influence of Build on Mortality."[5] It was not the intention of the editors to undertake an extensive study similar to that of the Medico-Actuarial Mortality Investigation but rather to endeavor to confirm the previous results or to obtain indications of any material differences that may have arisen. The methods of investigation in the two studies were practically the same; however, for ages 20 and over the Medical Impairment Study had available about one-half as much material (371,000 cases) as the Medico-Actuarial Mortality Investigation. The policyholders were again divided into three groups: overweight, standard and underweight. The mortality rate is given as "deaths per 100,000 exposed to risk."

For men accepted for insurance between the ages of 30 and 44 the subsequent mortality rates for cancer of the overweight, standard and underweight groups were 34, 37 and 49, respectively; for the age group of 45 years and over the figures were 176, 152 and 175, respectively. The difference apparent in the results of the Medico-Actuarial Mortality Investigation and the Medical Impairment Study is most perplexing in this review of the available insurance studies.

"Cancer and Diet."—For many years Hoffman has been a prolific worker in this field, and in 1937 he published an extensive book[6] dealing with the various phases of cancer and diet. He reviewed a great amount of literature, much of it confusing and conflicting. This material, coupled with results based on 2,234 questionnaires for living cancer patients and 1,149 questionnaires for noncancerous controls, caused him to conclude that "overnutrition is common in the case of cancer patients to a remarkable and exceptional degree, and that overabundant food consumption unquestionably is the underlying cause of the root condition of cancer in modern life." I am in general agreement with the first part of this conclusion, but believe that the causal relation stated in the second part is not based on adequate evidence.

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5. Supplement to Medical Impairment Study, New York, Actuarial Society of America and Association of Life Insurance Directors, 1932.

6. Hoffman, F. L.: Cancer and Diet, Baltimore, Williams & Wilkins Company, 1937.

Metropolitan Life Insurance Company Records.—In 1938 and 1939 Dublin and Marks published two articles on the mortality of women according to build, one based on "standard [7] experience," [8] the other on "substandard [7] experience." [9]

In the first study the mortality tables were based on 302,228 policies of standard experience, issued during the period from 1922 to 1934. The authors concluded that the cancer mortality rate displayed a tendency to rise with increasing weight. This relationship was most marked at the older ages, especially for cancer of the female genital organs and of the intestines. There was no distinct trend according to weight for cancer of the breast, stomach, liver and gallbladder.

The study of substandard experience was based on 121,248 policies for women, issued during the period from 1922 to 1934. Cancerous

Summary of Insurance Studies

Year	Author	Source of Material	Conclusions
1913	Title: "Medico-Actuarial Mortality Investigation"	Contributing Insurance Companies	Cancer mortality increases with increasing body weight
1929	Dublin	Union Central Life Insurance Company	Cancer mortality increases with increasing body weight
1929	Dublin	Metropolitan Life Insurance Company	A high percentage of those dying from cancer are overweight
1932	Title: "Medical Impairment Study"	Contributing Insurance Companies	No clear relationship between cancer mortality and body weight
1937	Hoffman	Questionnaires of hospitalized patients with cancer	Overnutrition is unusually common in histories of cancerous patients
1938-9	Dublin and Marks	Metropolitan Life Insurance Company	Cancer mortality increases with increasing body weight (true for some sites but not for all)
1939	Hunter	New York Life Insurance Company	Cancer group has a higher average weight than control group

women on the whole showed no distinct variation in mortality according to weight. A segregation of cases according to individual sites of tumors showed, for cancer of the liver and of the gallbladder and for benign tumors of the uterus, a distinct trend of mounting mortality with increase of weight.

New York Life Insurance Company Records.—In 1939 Hunter [10] published an analysis of life insurance experience with 3,239 cancer

7. A standard risk is an average good risk, i. e., a person having the normal life expectancy and acceptable at regular premium rates. A substandard risk is a below average risk, i. e., a person whose life expectancy is impaired and who is acceptable only at increased premium rates.

8. Dublin, L. I., and Marks, H.: Proc. A. Life Insur. M. Dir. America **24**:47, 1938.

9. Dublin, L. I., and Marks, H.: Proc. A. Life Insur. M. Dir. America **25**: 203, 1939.

10. Hunter, A.: Tr. Actuar. Soc. America **40**:394, 1939.

deaths. He compared the weights of persons dying from cancer with those of a corresponding control group of living policyholders. The comparisons were based on the percentage deviations of the weights of the policyholders with respect to the averages for the sex and ages at issue of policies. The cancer deaths were divided into separate groups, according to the sites of the tumors.

Hunter found that the cancer death group had an average weight higher than that of the control group. For men this value was + 1.7 per cent, and for women it was + 3.2 per cent. Hunter concluded that overweight is a factor affecting cancer incidence unfavorably.

In the table the conclusions of the statistical analyses have been brought together, showing in general that overweight persons have a distinctly greater tendency toward cancer.

COMMENT

Although the results of experimental work with animals and the analyses of insurance statistics strongly suggest that body weight is a factor affecting cancer incidence, there are many considerations that must be critically studied and evaluated before the fundamental nature of the relationship is fully understood. The weight of an animal or a human being is the result of many complex, often interrelated factors, such as the racial and hereditary characteristics, the qualitative and quantitative composition of the diet, the hormonal balance, the basal metabolic rate, exercise, previous health, and many others. One cannot be certain that the relationship between cancer and weight as discussed in this paper is necessarily a direct, primary one. It may be, and in uncompleted experimental work there is evidence for it, that some of the factors controlling weight are of more direct significance than weight itself, the latter being merely a resultant of these forces.

There are other possible sources of human statistics in which the relationship between cancer incidence and weight may be studied. For example, in the Veterans' Facilities there have been many hospitalized cancer patients whose records might be analyzed with reference to suitably selected controls. Other army and navy records, as well as the records of persons exposed to industrial and occupational tumors, could also afford material for study.

Analyses of human statistics, however, cannot have the accuracy of animal investigations, in which one may utilize pure strain mice, of known genetic composition, living in the same laboratory, where age, temperature, weight, diet and factors of cancerigenesis can be controlled. Furthermore, in an experimental investigation on animals, one may study a single type of tumor, in contrast to most studies on man, in which all types of cancers are grouped together. It has been pointed out, and is definitely accepted by workers in the field of tumors, that cancer

is not a single entity but a group of conditions. In this respect cancers may be considered to be a group of diseases as divergent as the many conditions that are classified as inflammations: boil, pneumonia, tuberculosis, scarlet fever, actinomycosis, etc. It may be that a correlation between weight and cancer exists for some types of tumors but not for all. Obviously, this is another complicating factor in human statistics, in which at best separation is made on the basis of organs or systems.

The inherent difficulties of studies on man and the comparative ease of obtaining animal material under controlled laboratory conditions suggest that further clarification of the basis of the relationship of cancer and weight is a problem of the laboratory.

The question might be raised regarding the validity of comparing the findings of the animal studies described here with those of insurance statistics, since my work mainly considered underweight and normal subjects, while the insurance studies dealt, in addition, with overweight subjects. Actually the terms "underfed," "underweight," "normal," "standard" and "overweight" are relative, for as yet there are no scientifically accepted standards for "normal" nutrition and weight. The important generalization that is brought out in the studies of both animal and human subjects is that cancer incidence is related to weight.

What is the practical significance of this apparent relationship of weight to cancer inception and incidence? If further critical, comprehensive studies should confirm the results reported here, it would appear that an important prophylactic measure has been brought to the attention of the medical profession. By establishing and maintaining weight levels at a minimum compatible with general good health (possibly 10 to 20 pounds [4.5 to 9 Kg.] below present "normal" levels), cancer may be prevented in a considerable number of persons in whom it would otherwise develop; at least, the cancer process might be delayed in time of appearance. Such a regimen is already known to affect beneficially other pathologic conditions, such as diabetes, heart disease, cerebral hemorrhage and other degenerative diseases.

One cannot emphasize too strongly that the conclusions drawn with regard to cancer and weight hold only for the prevention of the initiation or inception of tumors and not for the treatment of cancer once it has developed. Animal experimentation [11] has definitely proved that underfeeding may cause tumors to stop growing or even to regress, but in my experience the animals so treated do not live any longer than controls on a full diet. In addition, it is known from human experience that cancer runs its course regardless of diabetes, starvation or loss of weight and that it regresses only in exceptionally rare instances. Thus, avoid-

11. Bischoff, F.; Long, M. L., and Maxwell, L. C.: Am. J. Cancer **24**:549, 1935. Tannenbaum.[1]

ance of overweight is a measure that might prevent the inception of a tumor but is probably of no value once the tumor has developed.

At the present time the two accepted methods for the treatment of cancer are surgical removal and irradiation. It has been said that even if all present knowledge were diligently and successfully applied in the attack on cancer, 75 per cent of the people having cancer would still die of this disease. For the prevention of cancer, society is limited at present to the removal of precancerous lesions and the avoidance of industrial and occupational hazards. Should avoidance of overweight be incontrovertibly proved to be effective, it would be another point of attack in the prevention of a disease that is progressively taking an increasing toll of human life.

SUMMARY

Cancer is the result of many extrinsic and intrinsic factors; probably one of these is body weight. In both animals and man it appears that individuals of average weight or less are not as likely to have cancer as those who are overweight. One of the main purposes of this publication is to bring this association of body weight and cancer incidence to the attention of the medical profession, so that further work may be initiated. The fundamental basis of the relationship still requires clarification. Establishment and maintenance of lower average weight levels are worthy of trial in the prevention of human cancer.

SQUAMOUS CELL CARCINOMA OF THE EUSTACHIAN TUBE

HAROLD L. STEWART, M.D.
BETHESDA, MD.
AND
MARSHALL M. LIEBER, M.D.
PHILADELPHIA

A primary neoplasm of the eustachian tube is exceedingly rare if one may judge from the published reports. In textbooks and monographs on diseases of the ear, nose and throat little or no mention of this lesion is made, and the condition is rarely considered clinically. The purpose of this report is to record a case of primary carcinoma of the eustachian tube, proved to be such at autopsy, and to review and analyze the cases of this condition described in the literature.

REPORT OF A CASE

W. R., a white man aged 50, was admitted to the Jefferson Hospital, Oct. 3, 1934, complaining of a lump in the left side of the neck and constant left-sided headache and earache. The patient first noticed a painless, freely movable enlarging mass beneath the left mandible about one year previously. Six months later he noted pain on palpation and on twisting the neck. About three months before admission to the hospital he began to have severe constant headaches in the left occipital region and left-sided earache. Physical examination showed a freely movable, painless mass of lymph nodes in the neck just below the left mandible. The left side of the palate was inflamed and tender. The clinical diagnosis was probable Hodgkin's disease or lymphadenitis. Laryngoscopic examination showed nothing abnormal in the laryngopharynx. There was a bulging forward and inward of the left pharyngeal wall at the level of the otopharynx and nasopharynx. This was due apparently to a part of the mass on the left side of the neck. Three weeks later the mass in the neck was excised. The specimen consisted of an irregularly shaped mass, 5 by 4 by 2.5 cm., of several lymph nodes, the largest of which measured 1.5 cm. in diameter; the large node had a soft, necrotic center, whereas the others were small, firm and gray. Microscopically, the lymph nodes were extensively infiltrated by masses of tumor cells, which were relatively large, flattened and oval shaped, with large deeply stained nuclei, a few of which were in mitosis. The cells were not sufficiently differentiated in the sections prepared by the rapid paraffin technic to make one sure of their type, but they resembled squamous epithelium, although no definite prickle cells were observed. In the larger nodes there was also an extensive inflammatory reaction with sup-

From the National Cancer Institute, United States Public Health Service, Bethesda, Md., and the Department of Pathology, Jefferson Medical College, Philadelphia.

puration and fibrosis. The diagnosis was malignant tumor of the cervical lymph nodes, probably metastatic carcinoma. The patient was discharged from the hospital October 13.

From this time until his death twenty-six months later he was admitted to the hospital on nine occasions, and in the intervals he was regularly observed once or twice weekly by various members of the outpatient clinic of the department of neoplastic diseases.

Nov. 19, 1934, the patient still complained of severe headache, ringing in the left ear and pain in the left shoulder. A small hard node was palpable below the lower margin of the scar in the neck. The bulging of the posterior pharyngeal wall was more marked. The lymph nodes in the axillas were enlarged, particularly those on the left side. Biopsy examination of the nodes in the right axilla showed slight hyperplasia of the lymphoid follicles and considerable proliferation of the endothelial cells of the sinusoids. There was nothing to suggest a neoplastic change, and a diagnosis of chronic lymphadenitis was made. December 6, a course of deep roentgen ray therapy was instituted to three areas of the neck, with a total of 2,360 roentgens (r) in each lateral area and 750 r anteriorly; the course of therapy was completed on Jan. 11, 1935. On the following day, a course of chemotherapy was instituted, the patient receiving six injections of a total of 2.12 mg. of metallic lead and 2.12 mg. of manganese over a period of two weeks. The blood lead level rose from a normal of 0.002 mg. to 0.012 mg. per 10 Gm. of whole blood at the end of the treatment. Prior to this the hemoglobin content of the blood was 81 per cent, the red cell count 4,650,000, the white cell count 6,900 and the color index 1.06; at the end of the course the corresponding figures were 58 per cent, 3,100,000, 3,200 and 0.93, respectively. There was occasional stippling of the red blood cells, occurring in approximately 1 cell per high power microscopic field. The pain and swelling in the pharynx disappeared.

Four months later, the patient again complained of pain in the left side of the neck, face and head. Roentgenologic examination of the paranasal sinuses showed irregular clouding and thickening of the lining membrane of the left maxillary antrum. October 29, a course of roentgen ray therapy was instituted, a total of 3,250 r being applied to each of two areas over the antrum, and was completed December 4. Roentgenologic examination of the sinuses, repeated one month later, showed little change in the left maxillary antrum and what appeared to be a polyp in the floor of the right antrum; the sphenoid sinuses appeared cloudy.

Jan. 11, 1936, the left sphenopalatine ganglion was given an injection of 95 per cent alcohol, and the pain disappeared for one hour. The next day a 1 per cent solution of procaine hydrochloride was injected into the scar in the neck but afforded no relief. Several days later the first cervical ganglion was given an injection of 95 per cent alcohol, and this was accompanied by some relief of pain. This procedure was repeated one week later, with only temporary relief of pain. An area of suppuration developed at the site of injection, which was incised and drained. March 5, a radical operation was done on the right maxillary antrum. The tissue removed consisted of two soft, smooth, pink polyps, the larger measuring 2 cm. in diameter. Microscopically, these proved to be benign edematous polyps. The pain abated only temporarily. March 22, another attempt was made to inject alcohol into the sphenopalatine ganglion. Two days later erysipelas of the face developed, which responded effectively to roentgen ray therapy. April 20, a radical operation was done on the left maxillary antrum. The lining membrane was thickened and fibrous and was removed in its entirety. Histologically, it consisted of chronically inflamed tissue. Following this procedure, the pain became worse; it was severe, continuous and always limited to the

left side, beginning on the forehead and extending backward to the occipital region. General neurologic examination at this time disclosed nothing relative to the condition, and no involvement of any of the branches of the fifth nerve could be detected. Ophthalmoscopic examination also gave negative results. June 30, the old scar in the left side of the neck was excised, but this afforded no relief. Attempts were made to inject alcohol into the maxillary branch of the trigeminal nerve and the supraorbital branch of the fifth nerve but with unsatisfactory results.

The patient was admitted to the hospital for the tenth time, November 30, complaining of complete loss of appetite and fever. On physical examination there were many coarse rales over the bronchi, and the cardiac sounds were of poor quality. There was intermittent spasticity of the right arm, ankle clonus of the left leg and a suggestion of a bilateral Babinski sign. Death occurred December 1.

Autopsy.—The autopsy was performed twelve hours after death. The combined gross and microscopic diagnoses were: (1) carcinoma, squamous cell type, primary in the left eustachian tube with extension in the connective tissue surrounding the corresponding internal carotid artery and internal jugular vein into the base of the skull and cranial cavity and with metastases to the cervical lymph nodes on the left side; (2) acute suppurative meningitis due to Streptococcus haemolyticus; (3) bronchopneumonia; (4) acute focal hepatitis; (5) chronic focal nephritis; (6) benign glandular hyperplasia of the prostate, and (7) chronic purulent sinusitis with benign polyps.

The body was that of a fairly well nourished elderly white man. The mucous membrane of the lips and the skin were covered with a discrete herpetic eruption. Several firm nodules were palpated in the left side of the neck.

The heart weighed 420 Gm. The myocardium was of good tone and showed no fibrosis. The endocardium was normal, and the valves appeared competent. The coronary arteries and the first portion of the aorta showed moderate atherosclerosis.

The lungs were deeply congested and edematous and contained several soft gray and red areas, which were slightly elevated above the surface. The pleura was smooth, glistening and not thickened. There was no lesion of the mucosa of the pharynx, larynx or trachea.

The spleen weighed 180 Gm. and was composed chiefly of soft red pulp, the follicles being indistinct.

The pancreas and adrenal glands appeared normal.

The liver weighed 1,760 Gm. It was soft, and the cut surface was pale, with indistinct lobular markings. The bile ducts were patent, and the gallbladder was normal.

The gastrointestinal tract was free of any visible change except for patchy areas of congestion of the mucous membrane of the stomach.

The kidneys were similar except for size, the right kidney weighing 100 Gm. and the left, 140 Gm. The capsules stripped readily, and the surfaces were smooth. On section the renal tissue was pale, slightly reduced in amount but proportionately divided between cortex and medulla. The pelvic fat was increased. The ureters and urinary bladder were normal.

The prostate was small and contained a few small soft gray nodular areas. The testicles and the remainder of the genital system showed no visible change.

The thyroid gland was normal in size and consistency. The entire organ was separate and distinct from the nodular lesions in the left cervical region referred to.

The brain weighed 1,300 Gm. Covering the meningeal surface at the base of the brain and extending in patchy areas over the side and vertex was a layer of thick green purulent exudate. The lateral ventricles were distended with thin granular fluid. The ependymal lining of the ventricles was studded with small bright red petechiae and in areas was covered with exudate. There was no evidence of any intracerebral lesion. The pituitary gland appeared normal.

The middle fossa of the skull was covered with thickened dura, which was firmly adherent to the underlying bone. On either side of the suture line uniting the left basilar portion of the occipital bone and the petrous portion of the left temporal bone was a small round area of bony erosion. The margin of the eroded area was lined by a small nodule of firm gray tissue. Tissue of similar appearance was also found surrounding the left internal carotid artery and extending through the jugular foramen on the left side, surrounding the jugular vein. This neoplastic tissue contained yellow necrotic areas, and parts of it were liquefied.

The paranasal sinuses were widely explored. The mucous membrane of the sphenoid and maxillary sinuses was slightly thickened. In areas the mucosa was covered with purulent exudate, and attached to the mucous surface were a few soft edematous polyps. There was no induration at their base, nor any ulceration of the mucous membrane or other change to suggest malignant transformation. The mucous lining of the mastoid cells and of the bony portions of the internal and external auditory canals was smooth and not ulcerated.

Up to this point in the postmortem examination all efforts to demonstrate the primary source of the malignant neoplasm were attended with negative results. All the sites in which a primary tumor might be expected to yield metastatic deposits in the cervical lymph nodes had been carefully examined but with negative results.

The bone at the left side of the base of the skull was next chiseled away. The neoplastic tissue surrounding the internal carotid artery and extending through the jugular foramen was traced downward to the left cervical region. Here there was found a mass 5 cm. in diameter, together with several enlarged firm lymph nodes. The main cervical tumor lay immediately beneath the junction of the left middle and posterior fossae of the skull, between the base of the skull and the posterior wall of the pharynx. It was irregular in shape and composed of firm gray tissue, which was densely adherent to the surrounding structures, including muscle, fascia, nerves and blood vessels.

With the examining finger in the pharynx, the cervical tumor could be palpated. There was no sign of thickening or of any break in the continuity of the mucous membrane of the pharynx. The tip of a probe introduced into the pharyngeal orifice of the eustachian tube emerged in the midst of the tumor mass in the neck. The membranous portion of the eustachian tube and the tumor mass were removed together. Cross sections of the tube showed its lumen completely filled with gray tissue, and in other cross sections the mucous membrane of the tube appeared thickened by gray tissue. No neoplastic tissue was noted in the osseous portion of this structure.

Microscopic Observations.—Sections obtained from the membranous portion of the eustachian tube (fig. 1) showed the surface partly lined by a single layer of columnar cells and partly by pseudostratified columnar cells; in some sections portions of the surface were bare of lining cells. The deeper tissues contained collectively cartilage, striated muscle, fat, serous and mucous glands opening on the surface and numerous small round cells. The small round cells formed nodular infiltrations in the fibrofatty tissue of the wall of the tube. The cartilage occurred in the form of irregular plates and rounded masses.

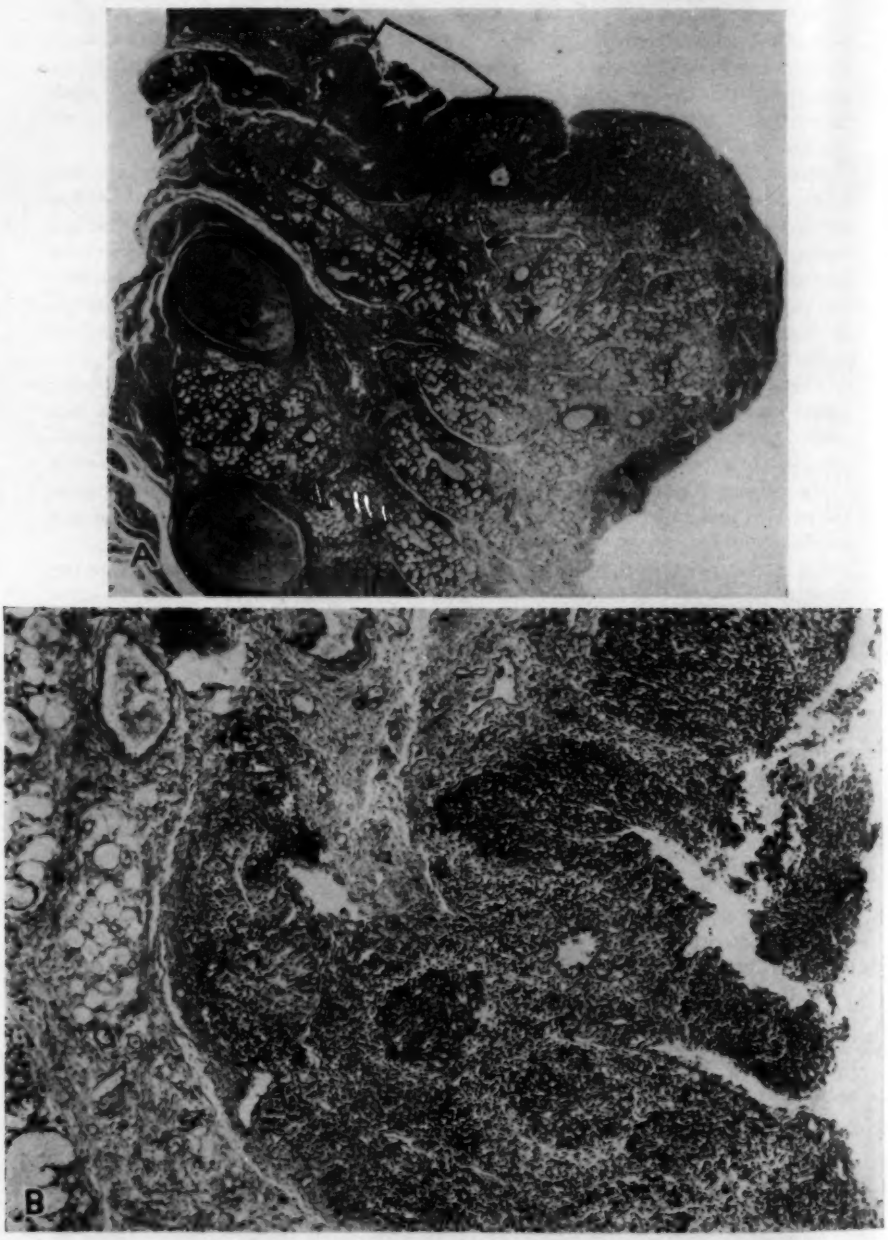

Fig. 1.—*A*, section through the eustachian tube; × 12. There is an infiltrating epitheliomatous area on the surface of the tube in the portion of the illustration which is marked off. *B*, surface of the eustachian tube marked off in A; × 72.5. There are groups of atypical tumor cells forming papillary excrescences on the surface and thickened masses in the deeper cryptlike formations.

Several of these sections of eustachian tube showed groups of atypical tumor cells forming elevated papillary excrescences on the surface and thickened masses basally in the crypts and in shallow ulcers. The atypical epithelial cells infiltrated the deeper tissues as thick expanding columns. In some areas the depth to which the malignant cells penetrated the underlying tissue appeared limited. Elsewhere, however, the tissues were deeply and widely permeated by the tumor cells, which showed perivascular and perineural extension resulting in separation of the cartilage plates and cartilage masses. A few blood vessels showing perivascular infiltration by tumor tissue were occluded by organizing thrombi.

Sections of the left internal carotid artery (fig. 2 *A*) and of other tissues obtained from the carotid canal were infiltrated with tumor tissue which showed a diffuse suppurative inflammatory reaction in the stroma. The artery showed advanced arteriosclerotic changes. A section of the left jugular vein and surrounding nerves and connective tissue taken from the jugular foramen similarly revealed neoplastic infiltration of the perivascular and perineural tissues. The inflammatory reaction here consisted mainly of small round cells.

The structural characteristics of the tumor were identical in the various locations in which it was studied, namely: the membranous portion of the eustachian tube; around the left internal carotid artery and left jugular vein and associated nerves, and in the cervical lymph nodes (fig. 2 *B*). The tumor cells were arranged chiefly in the form of large irregular sheets and broad columns of cells, separated by wide bands of connective tissue. The majority of the cells appeared polygonal, irregularly round or elongated and spindled, and although the cell boundaries were frequently difficult to distinguish with certainty, a few cells showed intercellular spines. The cytoplasm of the cells was acidophilic and sometimes finely vacuolated. Most of the nuclei were oval or round and tended to stain uniformly and moderately deeply with hematoxylin. A small number of the cells were of giant size, with lobulated, hyperchromatic and irregular nuclei. Sometimes two or more giant nuclei were contained in a single cell. Only a few mitotic figures were observed. Small epithelial pearls were very numerous in the areas of tumor tissue, and there were large wavy masses of loose keratin material interspersed among the tumor cells, some of which were necrotic. The tumor showed more keratinization in the lymph nodes than in other locations. The stroma was dense and hyalinized in most areas and contained many small capillaries and lymphocytes.

Sections of the mucous membrane of the pharynx and paranasal sinuses showed no evidence of malignancy. The mucous membrane of the latter showed a chronic suppurative inflammatory reaction and small benign polyps.

REVIEW OF THE LITERATURE

Negri,[1] in 1888, was the first to report a case of primary carcinoma of the eustachian tube. He gave a remarkably clear and detailed account of his patient, whom he observed over a period of four years, and he arrived at a correct clinical diagnosis. He described a syndrome consisting of unilateral headache, buzzing in the ear, trigeminal neuralgia, paralysis of the common oculomotor nerve with ptosis of the eyelid and exophthalmos. A biopsy specimen showed neoplasm, and the autopsy, which was limited to the head, was reported in detail. At the base of the brain, in the temporal-sphenoidal area was a small tumor, 3 by 2 cm., in the space between the sphenoid and the apex of the petrous bone. The neoplasm was directed medially and anteriorly to the sphenoidal fissure. There was extension to,

1. Negri, S.: Riv. oto-neuro-oftal. **12**:515, 1935.

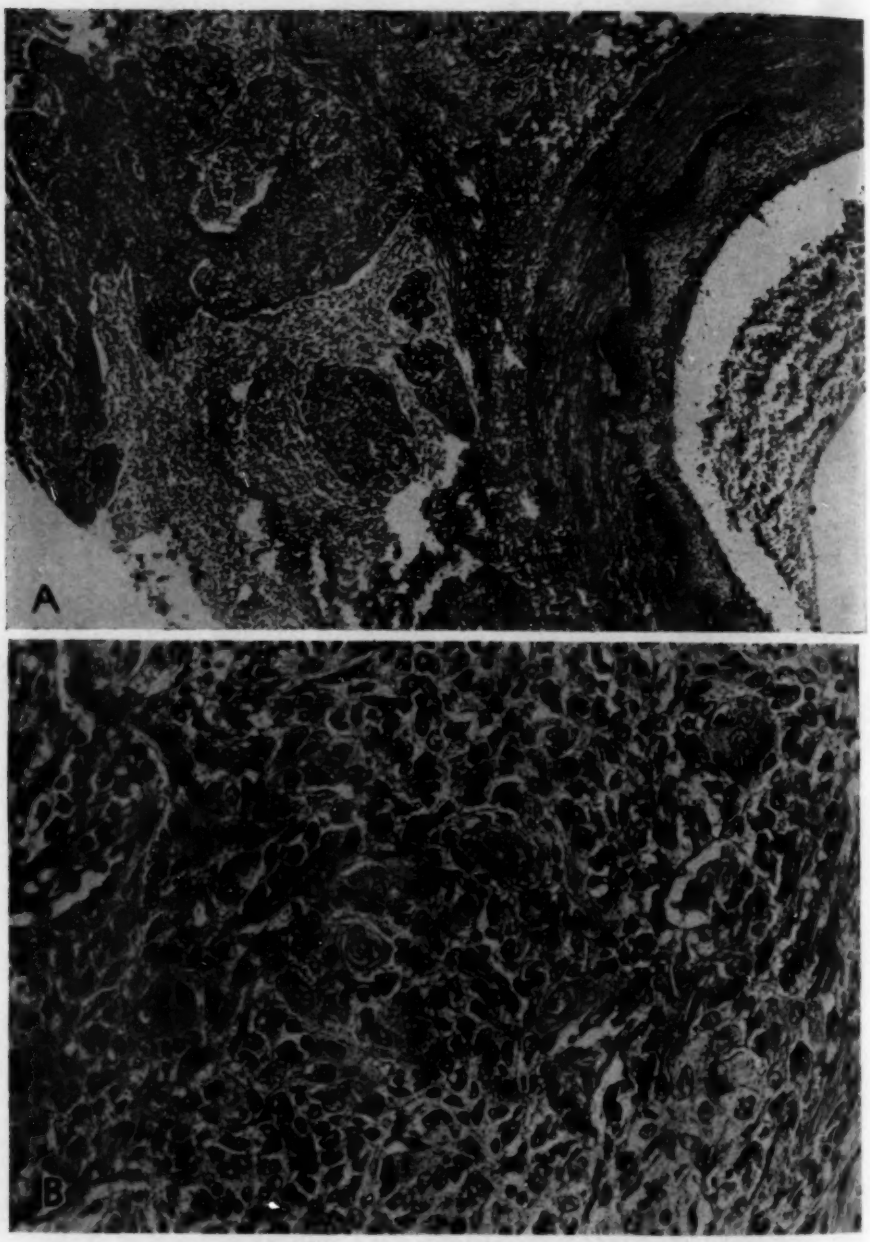

Fig. 2.—*A*, internal carotid artery showing infiltration of neoplasm in the connective tissue surrounding the vessel; × 95.5. *B*, metastatic deposit in a cervical lymph node showing the cellular characteristics of the tumor and pearl formation; × 298.

with enucleation of, the bulb. Corresponding to the pavilion of the eustachian tube and the left portion of the fossa of Rosenmüller was an irregular yellowish tumor mass with ulceration. The pavilion of the tube was destroyed in its inferior portion. Since the tumor was adherent to the body of the sphenoid, it was not possible to trace out the branches of the trigeminal nerve.

Proctor [2] in his case 1 found the left eustachian tube occluded by soft granulations, which bled easily. The lymph nodes in the right side of the neck became enlarged, indurated and tender. Later a mass was palpated around the left eustachian eminence. Biopsy examination revealed a rapidly growing carcinoma. Owing to the pain in the neck, practically all the structures in the right side of the neck were removed. The patient died about seven months after the onset, apparently from cerebral involvement, the growth appearing to have extended into the cranial cavity through the jugular foramen.

Jacod [3a] reported 2 cases of primary neoplasm of the eustachian tube in 1915. Case 1 was that of a man aged 68, who complained of buzzing and almost complete deafness in the left ear, pain in the left temporal area and loss of appetite. The eustachian cushion showed marked projection into the cavity of the tube, and a firm, circumscribed tumor was palpated in the area, covered by thickened mucosa, which was not ulcerated. The mass gradually increased in size until it occupied all of the lateral wall of the nasopharynx. Five weeks after the onset the superior maxilla was resected. The tumor was easily detached from the base of the skull, to which it was adherent. The neoplasm was ovoid and small and appeared to arise from the cartilaginous portion of the eustachian tube, which was involved in its entirety. One month later a chain of enlarged carotid nodes was removed. The neoplasm recurred in the nasopharynx, and death ensued five months after the onset. Histologically, the neoplasm was a small round cell sarcoma infiltrating the entire wall of the cartilaginous portion of the tube.

Case 2 was that of a man aged 53, who complained of buzzing and diminution of hearing in the left ear, a sensation of obstruction in the left nostril, constant dryness of the pharynx, and severe pain in the left ear and nasopharynx radiating to the left side of the head. Repeated examinations showed deformity and a reddish induration in the region of the left eustachian tube, which gradually increased in size. The tumor became large, firm, immobile and produced complete obstruction of the left naris. At operation the superior maxilla was resected, and a firm tumor without ulceration was disclosed, appearing to develop from the cartilaginous portion of the tube. The tumor was ablated as completely as possible. The histologic report was small round cell sarcoma. The tumor recurred two months later together with involvement of the regional lymph nodes. The patient died six months after the onset of symptoms and three months after operation.

The same author [3b] reported 2 more cases in 1921. Case 1 concerned a man aged 68, who complained of ocular difficulty, obstruction of the left nostril, impairment of hearing, with echoing of the voice and buzzing in the left ear, followed by violent and continuous headache having the character of trigeminal neuralgia, and hypesthesia of the left cheek. The ocular trouble consisted of impairment of vision, followed by diplopia and finally total loss of vision in the left eye. Otolaryngologic examination showed narrowing of the posterior nasal fossa. The left pharyngeal wall projected inward somewhat, and the left eustachian tube appeared to be tripled

2. Proctor, P. C.: Boston M. & S. J. **166**:96, 1912.

3. Jacod, M.: (*a*) Rev. de laryng., d'otol. et de rhinol. **3**:169, 1915; (*b*) Rev. neurol. **37**:33, 1921; (*c*) Ann. d'oto-laryng., February 1936, p. 215.

in size. The mucosa was infiltrated but not ulcerated, and a firm tumor was palpated in the region of the cartilaginous portion of the tube. There was a decrease in air conduction on the left side with an increase in osseous conduction. Examination of the eyes showed complete left ophthalmoplegia, total paralysis of the fourth and sixth nerves bilaterally, partial paralysis of the common oculomotor nerve, complete paralysis of the right internal rectus muscle of the eyeball, partial paralysis of the right superior and inferior recti and complete paralysis of the pupillary sphincter. The sympathetic nerves were not affected. Biopsy of the tumor showed a small round cell sarcoma. Seventy-eight milligrams of radium was inserted into the left nostril for three hours and again for twenty-two hours. The neoplasm decreased in size until it was no longer visible in the nasopharynx. The pain was relieved; it was again possible to breathe through the left nostril, and hearing was improved. However pain reappeared one month later, and the patient died about six months after the onset of symptoms and one and one-half months after the application of radium.

Case 2 was that of a man aged 32, who complained of violent pain in the region of the three branches of the trigeminal nerve, intense headache and difficulty in the left eye. There was total left ophthalmoplegia with paralysis of the common and external motor nerves and almost complete loss of vision. There was impairment of hearing in the left ear, and there was nasal and retronasal pain. A tumor was found arising from the left wall of the nasopharynx. Later the neoplasm extended through the zygoma into the left temporal region, and the patient died six or seven months after the onset of symptoms. Necropsy revealed a large sarcoma of the nasopharynx extending to the left anterior cerebral fossa, having eroded the bone in front of the labyrinth, encircled the pocket of dura mater at Meckel's cavity and the cavernous sinus, penetrated into the orbit and the sphenoidal fissure and involved at this level all the cranial nerves, which were tensely stretched over the tumor.

Charleux, Mounier-Kuhn, Feuillade, Girard and Lévy [4] in 1935 reported a case of carcinoma of the eustachian tube in a man aged 60. The onset occurred eight or ten months before, with violent pain localized in the left ear, extending later to the left side of the face and head, particularly in the temporoparietal region, with radiation toward the nape of the neck. There was also a sensation of deep soreness on breathing through the nose. Later ocular difficulty appeared, with diplopia and impairment of vision. He found it necessary to hold his hand to the left eye in order to see, read or get about. He had irregular periods of slight epistaxis. There was paralysis of the left external oculomotor and sixth nerves. The uvula was directed toward the right in phonation. The tongue was deviated toward the left. There appeared to be lessening in the motility of the left vocal cord. There were definite involvement of the fifth and sixth nerves and doubtful involvement of the seventh, ninth, tenth, and eleventh nerves. A tumor was noted in the region of the left eustachian tube, and salpingoscopy showed a vegetating reddish growth in the region of the pavilion of the tube. Biopsy showed a prickle cell epithelioma. The patient received radium therapy, which gave marked relief of pain but did not appear to modify the tumor. No further record of this patient was available.

Jacod [3c] reported an additional case in 1936. A man aged 40 complained of pain in the left ear and slight, intermittent temporal headache. A catheter passed into the left eustachian tube met with marked obstruction and when removed was covered with blood. The pavilion of the tube was tumefied at the level of the anterior cushion. The thickening of the peritubular tissue also extended toward the fossa

4. Charleux; Mounier-Kuhn; Feuillade; Girard, and Lévy, A.: Lyon méd. **155**:399, 1935.

of Rosenmüller. There was no cervical enlargement. Biopsy of a portion of the tumor showed a reticular tissue containing many plasma cells, lymphocytes, polynuclear cells and especially cells of the histiocytic type, many of which showed mitoses and certain of which also showed giant nuclei. The diagnosis was histiocytic or reticulum cell sarcoma. The patient was given a course of roentgen ray therapy, receiving a total of 2,200 international units over a period of three weeks. Three months later a transverse maxillary incision was made, and the posterior portion of the nasal septum was resected. After circular section of the soft peritubular tissues, a funnel resection of the tube together with its cartilaginous portion was done. Further notes as to the subsequent fate of the patient were not recorded.

Fürstenberg [5] in 1938 reported a case that concerned a man aged 34. He complained of fulness in one ear. Examination failed to disclose a lesion in the nasopharynx, although the presence of one was suspected because of metastases to the cervical lymph nodes. Repeated biopsies of tissues from the nasopharynx in the region of the eustachian tube failed to reveal primary cancer. Postmortem examination showed extensive destruction of the base of the skull and a carcinoma within the eustachian tube, but no invasion of the nasopharynx.

Other reports indicating a possible malignant neoplasm having origin in the eustachian tube are those of Abbott,[6] Jones,[7] Law,[8] Brown,[9] Proctor [2] (case 2), Salinger and Pearlman [10] (tabulated under slide numbers 913, 1327 and 5742), Becco [11] and Hauser and Brownell [12] (case 4). Incidentally, a case of fibroma of the eustachian tube was reported by Hunt [13] in 1926.

AGE AND SEX; INCIDENCE

Among the 10 patients whose cases comprise this series there were 9 men, ranging in age from 32 to 68 years, with an average of 52.5 years, and 1 woman, aged 53 years.

From an extensive review of the literature on carcinoma of the nasopharynx or epipharynx it appears that in only a few of the reports was the exact location of the tumor stated on first examination. For example, in 12 of the 24 cases of malignant tumor of the epipharynx reported by Salinger and Pearlman [10] there was a definite record of either the eustachian tube or the fossa of Rosenmüller being the seat of growth. Similarly in the majority of the reports reviewed it was simply stated that a neoplasm was found about the orifice of the eustachian tube or in the fossa of Rosenmüller with involvement of the former. Pathologists rarely explore the region about the eustachian tube at autopsy, nor is it possible to do so routinely. Not infrequently, at postmortem examination a tumor is present in the neck in a case in which

5. Fürstenberg, A. C.: Surg., Gynec. & Obst. **66**:400, 1938.
6. Abbott, F. C.: Tr. Otol. Soc. U. Kingdom **2**:18, 1901.
7. Jones, J. A.: Proc. Roy. Soc. Med. (Sect. Otol.) **3**:55, 1910.
8. Law, E.: Proc. Roy Soc. Med. (Sect. Otol.) **3**:28, 1910; **4**:67, 1911.
9. Brown, C. M.: Laryngoscope **22**:37, 1912.
10. Salinger, S., and Pearlman, S. J.: Arch. Otolaryng. **23**:149, 1936.
11. Becco, R.: Rev. Asoc. méd. argent. **50**:1581, 1936.
12. Hauser, I. J., and Brownell, D. H.: J. A. M. A. **111**:2467, 1938.
13. Hunt, J. G.: Arch. Otolaryng. **8**:363, 1926.

the primary site has not been detected clinically or at autopsy. It is possible that in a significant number of such cases, if dissection were carried out more carefully at autopsy, the primary site would be disclosed in the eustachian tube.

Of considerable interest is a recent paper by Dunlap [14] in which he called attention to the great frequency of malignant tumor of the nasopharyngeal opening of the eustachian tube and of the tube proper in China. He observed 16 cases of the disease in six years of private practice in Shanghai and stated that numerous persons with such tumors appeared for examination and treatment in the clinic of the Peking Union Medical College. Forty per cent of the author's practice was among the Chinese, and all the patients with this disease observed by him were Chinese or other orientals. Most of these patients had a history of deafness, hemorrhage or nasal obstruction, and in most of them metastases occurred. Virtually all the biopsies made showed a low grade transitional cell epithelioma, which appeared radiosensitive. Unfortunately, Dunlap [14] published no individual case reports.

MORBID ANATOMY

A biopsy specimen only was obtained from the eustachian tube in 4 cases, and no further details were presented except in a case in which death was apparently due to cerebral involvement from extension of the growth through the jugular foramen. In 2 additional cases operation revealed a small firm ovoid tumor mass attached to the base of the cranium and arising from the cartilaginous portion of the tube. Necropsy was performed in the cases reported by Negri,[1] Jacod [3] (case 2, 1921) and Fürstenberg [5] and by us. It is apparent that in each instance the neoplasm arose from the cartilaginous portion of the eustachian tube. There was a small firm tumor attached to the base of the skull in the temporosphenoidal area with early extension into the middle or anterior cerebral fossa through the jugular foramen or sphenoidal fissure. The cranial nerve trunks at this level were compressed, with resultant paralysis, particularly of the fifth and sixth nerves and occasionally of the second, third and fourth nerves. Extension of the growth into the sphenoidal fissure and orbit was responsible for the ocular syndrome observed in some of these cases. It is interesting that in Fürstenberg's [5] case there was extensive destruction of the base of the skull without, however, invasion of the nasopharynx. Similarly, in our case the mucosa of the nasopharynx was not found invaded at postmortem examination. Enlargement of the regional cervical lymph nodes occurred in 5 cases, and metastatic involvement of these nodes appeared early in at least 3 of these cases. There was no record of more distant metastases in any case.

14. Dunlap, A. J.: Chinese M. J. **53**:68, 1938.

HISTOLOGIC CHARACTER

Jacod [3] designated his 5 specimens as sarcoma, 4 being described as small round cell sarcoma and 1 as a reticulum sarcoma. Negri,[1] Proctor [2] and Fürstenberg [5] supplied no histologic details, stating simply that the growth was a carcinoma. Charleux and co-authors [4] reported their finding as a prickle cell epithelioma. Our tumor, described in detail, was a squamous cell carcinoma.

The literature is full of confusions and contradictions in the designation of nasopharyngeal growths. Ewing [15] and Salinger and Pearlman [10] adequately reviewed and discussed the histologic features of these tumors. According to Ewing,[15] it is at times difficult to decide whether to classify a given specimen as epithelioma, transitional cell carcinoma or lymphosarcoma. Salinger and Pearlman [10] stated that most of the nomenclature has been in error and that many of the tumors of the nasopharynx heretofore termed sarcoma were in reality transitional cell carcinoma or lymphoepithelioma.

CLINICAL FEATURES

No history of symptoms was supplied in Proctor's [2] case, and the only symptom in Fürstenberg's [5] case was a feeling of fulness in one ear. In the remaining 8 cases a prominent symptom was intractable pain. Headache appeared as the first symptom in 3 cases, occurring later in the others. It usually began in the temporal area and on the side of the face, and in 4 cases it was described as having the character of trigeminal neuralgia. The pain usually increased in severity, becoming constant and violent terminally. It was associated with pain in the ear in 4 cases and was followed by nasal, retronasal and nasopharyngeal pain in 3 cases. Pain in the neck occurred as a late symptom in 2 cases.

Symptoms referable to the ear were present in each of the 8 cases. Diminution in acuity of hearing was an early symptom in 6 cases, together with buzzing in 3 cases. Pain was the only aural symptom in 2 cases, although it also occurred in 2 other cases included in the 8 cases. Auditory symptoms ushered in the disease in 5 cases, either alone or in association with headache.

Symptoms referable to the eye occurred in 4 cases. These consisted of dimness of vision, diplopia, ophthalmoplegia and total blindness. These appeared early in only 1 case. Evidences of partial or complete paralysis of the fourth and sixth nerves were present in all these cases.

Epistaxis occurred in only 2 cases and was slight in amount. Nasal obstruction was complained of in 2 cases.

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15. Ewing, J.: Am. J. Path. **5**:99, 1929.

PHYSICAL FINDINGS

Evidence of involvement of the eustachian tube or of the otopharynx was present in 9 cases; repeated examination of these areas in Fürstenberg's [5] case gave negative results. A firm, immobile tumor at the level of the tubular eminence or anterior cushion was detected in 7 cases, usually with inward or forward bulging of the pharyngeal wall at this level. The latter only was noted in our case. In Negri's [1] case the only sign noted was ulceration of the mucosa lining the choana in the region of the pavilion of the tube. Ulceration was not a feature in the other cases. Salpingoscopy showed evidence of complete obstruction of the tube in 6 cases. Extension of the growth into the otopharynx, i. e., toward the fossa of Rosenmüller, was noted in only 1 case.

Otoscopic examination was performed in 6 cases, 4 of which were reported by Jacod.[3] Apparently the only changes of note were retraction of the drum head and slight redness of the tympanum. Jacod [3] stated that in his cases the tympanum had the appearance of that in ordinary catarrhal otitis with or without effusion.

Enlargement of the lymph nodes in the neck was noted in 5 cases. In Proctor's [2] case, although the primary neoplasm was on the left side, enlargement of the lymph nodes occurred on the right side. In his case the lymph nodes became indurated, tender and painful and were therefore removed. In Fürstenberg's [5] case metastases to the cervical lymph nodes occurred early, and it was because of this finding and that of a feeling of fulness in one ear that a neoplasm in the eustachian tube was suspected. In our case a painless, freely movable mass beneath the left mandible was the first sign, noted by the patient approximately one year before his first admission to the hospital. Six months later he noted tenderness and pain on palpation or twisting of the neck. Three months after that he began to complain of severe headache and earache.

DIAGNOSIS

A clinical diagnosis of neoplasm of the eustachian tube or of the otopharynx was correctly made in 9 cases and substantiated at biopsy in 6 of these. In our case the eustachian tube was at no time suspected as a possible source of the primary neoplasm during the life of the patient.

It is our belief at present that the only circumstances in which a diagnosis of carcinoma of the eustachian tube can be confidently affirmed is when complete autopsy has established the absence of all possible primary neoplasms in the craniocervical area and in all other parts of the body which are likely to yield metastatic deposits in the cervical lymph nodes.

TREATMENT

Medical treatment only was carried out in 3 cases. Negri's [1] patient lived for about four and one-half years, and Jacod's [3] patient (case 2, 1921) lived for six or seven months from the onset of symptoms to the time of death. Fürstenberg [5] made no mention as to the form of treatment or the duration of the illness.

Surgical therapy was instituted in 5 cases. In Proctor's [2] case the glands in the neck were excised because of pain in that region, which was relieved. The patient died five months after operation or seven months after the onset of the disease. In Jacod's [3a] case 1, 1915, the superior maxilla was resected, and the tumor was easily detached from the base of the cranium, to which it was adherent. The tumor was ovoid, the size of a nut, and arose from the cartilaginous portion of the tube, which it involved in all of its length. One month later a second operation was performed for removal of enlarged lymph nodes in the neck. One month after this, local recurrence of the growth was noted in the nasopharynx. The patient died five months after the onset of the disease or four months after the first operation. In Jacod's [3a] case 2, 1915, resection of the superior maxilla was done, followed by ablation of as much of the tumor as possible. The neoplasm was firm and not ulcerated; it had developed from the cartilaginous portion of the tube. Recurrence with involvement of local lymph nodes occurred two months later. The patient died three months after the operation or six months after the onset of symptoms. In Jacod's [3c] case published in 1936 a transverse maxillary incision was made, with resection of the posterior portion of the nasal septum. After circular section of the soft peritubular tissues, a funnel-shaped resection of the cartilaginous portion of the tube was carried out. No further data were recorded, and nothing was said about the subsequent fate of this patient. It is interesting in this case that roentgen ray therapy was instituted two months before operation, a total of 2,200 international units being applied. In our case the mass in the neck was excised. About one and one-half years later, radical resections of the mucous membrane of the right and left maxillary antrums were performed one and one-half months apart. Two months after this, an old scar in the left side of the neck, the result of incision for obtaining a biopsy specimen, was excised because of pain. No relief of symptoms was afforded by any of these operations, and the patient died twenty-five months after the first operation or about three years after the onset of the disease.

Roentgen ray or radium therapy was employed in 3 cases in addition to Jacod's [3c] case, mentioned. In Jacod's [3a] case 1, 1921, two tubes containing 78 mg. of radium were placed in the left nostril, one remaining for three hours and the other for twenty-two hours. This was followed

by relief of pain, reduction in the size of the tumor and ability to breathe through the nostril. Hearing was improved, and finally no evidence of the tumor could be detected. However, one month later the pain reappeared, and the patient died about two weeks after that or six months after the onset of the disease. With regard to the case observed by Charleux and colleagues,[4] no details as to the form or the dose of radium therapy are given, but there was marked amelioration of the symptoms even though the tumor in the temporal fossa did not appear to be modified. No further details as to the subsequent fate of this patient are given. The onset of the condition had occurred about ten months before radiation therapy was instituted. Our patient received an intensive course of roentgen ray therapy, followed by intravenous chemotherapy. The details of the treatment are noted in the accompanying history. Following the use of radiation, the pain and the local swelling in the pharynx disappeared. Four months later pain recurred in the head and the left side of the neck. A second course of roentgen ray therapy was instituted over both antral areas nine months after the first course of treatments, but the symptoms persisted despite injections of alcohol into the sphenopalatine and first cervical ganglions and into the maxillary branch of the trigeminal nerve and the supraorbital branch of the fifth nerve. The patient died two years after the first course of roentgen ray therapy or about three years after the onset of the condition.

SUMMARY

A clinical and pathologic study of a case of carcinoma of the eustachian tube is presented, together with a review of the literature on tumors of this structure.

CHEMICAL ANALYSIS OF LIVER IN A CASE OF ESSENTIAL XANTHOMATOSIS

HAROLD WOOD, M.D.
AND
HAROLD REINSTEIN
BOSTON

When the original report [1] of this case was prepared for publication, facilities were not available for a chemical analysis of tissue. Since then the few available grams of liver, free of tumor, has been analyzed for the fractional lipid content by the method developed by Thannhauser

A Comparison of the Fractional Lipid Content of Liver from a Fourteen Month Old Infant with Essential Xanthomatosis with That of Normal Liver

	Liver from Patient *	Normal Human Liver *
Total cholesterol	7.25	Approx. 0.93
Free cholesterol	2.70	Approx. 0.34
Ester cholesterol	4.55	Approx. 0.59
Total phospholipids	7.40	Approx. 9.80
Sphingomyelin	0.19	Approx. 0.38
Cephalin	5.21	Approx. 4.62
Lecithin	2.00	Approx. 4.81
Total lipoid fatty acids	9.05	Approx. 10.00

* The values are expressed as milligrams in 100 mg. of dried tissue.

and his associates.[2] This tissue had been preserved from March 1936 to June 1939 in Kaiserling's solution I [3] and/or in solution of formaldehyde U. S. P. diluted 1:10. No splenic tissue was available for analysis. In the accompanying table the results are compared with the fractional lipid content of normal liver as determined by this method.

A striking aberration from the normal occurs in the total cholesterol, which is increased over seven times. Both the free cholesterol and the ester cholesterol are decidedly increased. The total of phospholipids is decreased, the sphingomyelin and lecithin are decreased, the cephalin is increased, and the total of the lipoid fatty acids is decreased.

From the Department of Pathology and Bacteriology, Tufts College Medical School, and the Medical Clinic of the Boston Dispensary.

1. Wood, H.: Arch. Path. **26**:873, 1938.

2. Thannhauser, S. J.; Benotti, J., and Reinstein, H.: J. Biol. Chem. **129**: 709, 1939.

3. The formula of Kaiserling's solution I is: formaldehyde, 200 cc.; water 1,000 cc.; potassium nitrate, 11 Gm.; potassium acetate, 21 Gm.

In contrast to the findings in the foregoing paragraph Niemann-Pick disease shows a high total of phospholipids and especially a high sphingomyelin content.[4] This is exemplified in a case of Niemann-Pick disease which was examined by Dr. S. J. Thannhauser and his associates, in which the total of the phospholipids of the dried liver was 37 mg. in 100 Gm., and the content of sphingomyelin, 26 mg. in 100 Gm.[5]

COMMENT

On the basis of the chemical analysis this case should be designated as one of essential xanthomatosis due to defective cellular cholesterol metabolism. The organs involved were the liver, spleen and lungs. There were no xanthomatous foci in the skin. The blood vessels were not involved. The bone and tendons were not examined. The child was not jaundiced. The liver was affected only by interspersed nests of xanthoma cells, and there was no granulomatous tissue in the liver or spleen.[6]

4. Klenk, E.: Ztschr. f. physiol. Chem. **229**:151, 1934.
5. Thannhauser, S. J.; Benotti, J., and Reinstein, H.: Unpublished data.
6. Thannhauser, S. J., and Magendantz, H.: Ann. Int. Med. **11**:1662, 1938.

General Reviews

OCCURRENCE AND SIGNIFICANCE OF CONGENITAL MALIGNANT NEOPLASMS

H. GIDEON WELLS, M.D.
CHICAGO

The experimental production of cancer has corroborated the clinical observation that ordinarily the exciting agent must act through a considerable portion of the life period of the victim. Hence the cancer of the dye worker and the pioneer x-ray technician usually appears seven to fifteen years after exposure is begun, i. e., one tenth to one fifth of the life expectancy, while in the dog the production of cancer by cancerigenic agents requires two or three years, in the rabbit six to eighteen months, and in the mouse, at least with most agents, three months or so, corresponding to about the same fraction of the usual duration of life. Presumably this is an important factor in making human cancer ordinarily a disease of the latter part of life, rather than that cancer is fundamentally a disease of old tissues, for among experimental animals cancer develops in young animals in response to cancerigenic agents quite as rapidly and readily as in old animals.

In glaring contrast to these statements is the fact that certain types of malignant growth are seen almost exclusively in the very young and that sometimes a malignant growth may develop in the fetus, even producing widespread metastases, before the brief span of intrauterine existence has been accomplished. Surely these tumors must differ in some fundamental way from the ordinary sorts of cancer, which require so long a period for development, and this difference may throw some light on the mystery of malignancy. Having observed in the necropsy material of this department malignant tumor tissues from 4 infants in whom the growths were present at the time of delivery, I was stimulated to look into the question of prenatal malignancy in the hope that something might be found which in the light of recent developments could offer some suggestions as to cancer genesis.

That cancer in some form may be present at or before birth is well known, but when an attempt was made to learn how, when and where such prenatal malignant neoplasms have occurred, the available literature

From the Otho S. A. Sprague Memorial Institute and the Department of Pathology, University of Chicago.

was found to be woefully unsatisfactory and unreliable. Complications there are, but too uncritical use has been made of the scattered reports on the few recorded cases. Many of them date back to medical literature of such ancient times that the recording physician attributed the infant's tumor to the mouse that ran across the mother's foot during the seventh month of pregnancy, yet his diagnosis as to the nature of the psychogenic neoplasm is accepted as reliable. Author after author has accepted the word of the preceding writer, and copied, with his own original deviations, the erroneous reference citations until it is absolutely impossible, even with the resources of the Surgeon General's Library and the help of zealous librarians, to locate all the original reports. The varied use of the word "infant" in different languages explains why a case cited repeatedly in the literature as one of cancer in an infant is found to have been a case of cancer in a 17 year old subject, and the fact that a cancer which has developed at 30 years of age in tissues present since birth is sometimes reported as a "congenital" cancer, e. g., a malignant tumor arising in a mole or a birth mark, adds to the confusion. Of course, as Nicholson said, "Birth is a mere incident in the life of the individual; therefore all tissues and tumors are essentially congenital."

In view of the importance of the subject it has seemed worth while to do a job of house cleaning and try to make as complete and reliable a review as possible on the basis of a study of the original reports and a critical consideration of the diagnosis as recorded by the reporter, rather than as accepted by a later doctorate candidate hustling to prepare the dissertation before the academic deadline arrived, or by a secretary providing the boss with "the best bibliography money can buy."

The tumors that are essentially those of infancy and early childhood are:

1. Neuroblastoma of the retina
2. Mixed malignant renal neoplasms ("Wilms' tumor")
3. Neuroblastoma of the adrenal and of other parts of the sympathetic nervous system

RETINAL TUMORS

Wintersteiner in his classic monograph "Neuroepithelioma Retinae," published in 1897, stated that of 467 cases, the disease was recognized in the first three years of life in 314 (67 per cent) and that in no less than 34 (7.3 per cent) it was present at birth sufficiently far advanced to have produced the so-called "amaurotic cat eye." Presumably this symptom was present in many of the other cases but was not observed. He said that probably all cases noted in the first year (102, or 22 per cent, in his series) and possibly all those of the second year (95, or

20 per cent in his series) were also to be considered as congenital, and ventured this statement, "I might even go so far as not to fear to assume that neuroepithelioma of the retina is always a congenital disease, although often the 'anlage' at the time of birth is so small that it would even escape ophthalmoscopic examination."

More recent observations have only strengthened Wintersteiner's position. Thus, Sattler stated that in over 80 per cent of instances retinal glioma was seen in the first four years of life and that in at least 7 per cent it was recognized at birth by the bright reflex from the pupil. Supporting facts are: (1) that there are pronounced familial occurrence and hereditary transmission; (2) that bilateral involvement is frequent (97, or 20 per cent, of Wintersteiner's cases) and that in the cases of bilateral involvement one eye may be demonstrably affected at birth, while the second eye may not exhibit the disease until months or even years later (Parsons); (3) that frequently there are multiple foci in the same eye in early cases.

Of much significance is the report of Seefelder that in no less than 7 otherwise normal eyes of premature fetuses (6 to 8 months) he found atypical cell complexes in the retina or optic nerve which were not completely differentiated and in 2 cases had led to tumor-like formations. And A. von Szily found that in the course of experiments to influence the development of chick embryos there appeared gliomatous malformations in the brain.

In view of these and other observations (e. g., Amolsch) it seems probable that gliomatous maldevelopments often take place in the prenatal development of the nerve tissues but that only few of them become malignant. The hereditary factor seems to be particularly important in tumors of the retina as compared with tumors of other nerve tissues.

The neuroblastic neoplasm of the eye is in glaring contrast to the other common ocular tumor, the melanoma, for I can find no report of a congenital malignant melanoma of the eye. Wintersteiner in 854 cases of retinal sarcoma (or melanoma) found only 20 growths reported in the first ten years of life, and of these, the ones in the youngest patients were pigment free and therefore probably not melanoma at all, but glioma. However, congenital melanosis oculi often becomes malignant in later years (Doherty). For example, Ewing (1928 b) mentioned a case he followed for ten years in which the lesion gradually extended, was twice excised and eventually became disseminated. Such growths are like those arising at various ages on pigmented moles present since birth. They are malignant growths arising on congenital lesions, but they are not congenital malignant tumors, although often indexed as such to the confusion of the literature.

CONGENITAL MALIGNANT RENAL TUMORS

Mixed tumors of the kidney constitute, next to the neurogenic neoplasms, the most abundant of the specific tumors of childhood. Of 100 malignant tumors encountered in a children's hospital, 21 were nephroblastoma (McCurdy). Ewing (1928 c) said, "The great majority of cases are observed in the first three years of life, it is rarely found after the tenth year, but Hedren reports a bilateral tumor at fifty-four years." Of 35 cases reported by Geschickter and Widenhorn, in only 5 were the patients over 5 years of age, 1 of these being a man of 40. In marked contrast is the more common renal tumor, the "hypernephroma," which practically never appears in childhood, and very rarely before the twentieth year. In the 84 cases in the Geschickter and Widenhorn series the youngest patient was aged 18, and only 4 others were below 30. Ladd, reporting on 58 cases of "embryoma" of the kidney observed in the Children's Hospital in Boston, stated that the records for twenty years contained no mention of a case of hypernephroma.

Nevinny reviewed the literature in 1926 and found that of 155 malignant renal tumors in children under 10 years of age, 11 were in fetuses or newborn infants, but of these 11, some must be eliminated as inadequately established.

In table 1 are listed the 5 tumors that seem to be, beyond reasonable doubt, congenital malignant nephroma. In table 2 are listed 11 more which probably belong in the same category but which are lacking some necessary proof that they are congenital malignant nephroma.

As to the origin of these tumors, Geschickter and Widenhorn made the following statement:

> Approximately two-thirds of all Wilms' tumors contain only those microscopic elements of spindle cells and early tubule formation which can be found in the normal embryonic kidney or in the zone of development just beneath the capsule of the kidney in normal infants and a few months after birth. The majority of these tumors, therefore, are neither teratomatous nor mixed, but represent a neoplastic exaggeration of the normal developmental processes occurring in the growth zones of the renal cortex in late fetal life or in the first few months after birth. For this reason the term embryonal nephroma (introduced by Feldman) is a particularly apt one for these neoplasms.
>
> The occurrence of cartilage, bone, or muscle in approximately one-third of these new growths is not strange when we consider that the more undifferentiated mesenchymal spindle cells found in the normal nephrogenic tissue in the process of development may retain the multiple potentiality for the elaboration of all the normal mesenchymal derivatives.

The almost exclusively infantile occurrence of these "embryonal nephromas" and their definite derivation from incompletely developed embryonic structures make them all in a sense congenital malignant neoplasms, but in how large a proportion the malignant transformation

TABLE 1.—*Congenital Malignant Renal Tumors*

No.	Age	Sex	Author	Type	Metastases	Size	Comment
1	30 cm. fetus	M	Dienst: Ztschr. f. gynäk. Urol. **4**: 45, 1913	Mixed tumor	0	Hen's egg	Typical adenomyosarcoma completely replacing right kidney; left kidney normal
2	Full term	F	Jacobi*: Collectanea Jacobi, New York, Critic & Guide Company, 1909, vol. 5	Sarcoma	0	Caused dystocia	Large nests of round cells surrounded by connective tissue
3	Fetus 7 mo.	F	Kästner: Frankfurt. Ztschr. f. Path. **25**: 1, 1921	Sarcoma	0	65 Gm.	"Pure spindle cell sarcoma"
4	Full term	?	Porter and Carter: Am. J. Dis. Child. **20**: 323, 1920	Sarcoma	?	Dystocia; 1½ times fetal head; embryotomy	Reported as round cell sarcoma but suggests embryonal nephroma
5	Full term	?	Semb: Centralbl. f. Gynäk. **4**: 1080, 1894	Mixed tumor	0	250 Gm.	Macerated fetus

* Reported in Tr. Internat. M. Cong., Copenhagen, 1884; abstracted, Jahrb. f. Kinderh. **25**: 112, 1886.

TABLE 2.—*Probable Congenitally Malignant Renal Tumors*

No.	Age at First Symptom	Sex	Author	Type	Metastases	Size	Comment
1	4 weeks	?	Braune: Arch. f. Kinderh. **112**: 193, 1937	Malignant nephroma	Brain	"Plum"	Cerebral symptoms at 4 weeks. Infant died at 4 months. Fist-sized metastasis in brain
2	Few days	F	Delon: Ann. d'anat. path. **15**: 435, 1938	Malignant nephroma	0	"Enormous"	Vomiting since birth. Abdomen swollen at 2 months. Tumor removed at 76 days. Patient well at 2 years
3	4 days	F	Delon: Ann. d'anat. path. **15**: 435, 1938	Malignant nephroma	0	120 Gm.	Vomiting at 4th day. Abdominal tumor noted on 26th day. Removed at 50th day. Infant well at 10 months
4	1 day	M	Deming: J. A. M. A. **80**: 902, 1923	Sarcoma	0	"Grapefruit"	Hematuria 1-4th days. Abdomen large since birth. Cystic. No mixed tumor elements
5	3 days	?	Häuptner: Ueber embryonale Adenosarkome der Niere, Inaug. Dissert., Greifswald, F. W. Kunike, 1907	Malignant nephroma	?	10×7×4 cm.	Infant died after nephrectomy at 5 months. Original article not available; cited by Nevinny
6	Few days	M	Jacobi-Leibert: Jahrb.f. Kinderh. **21**: 276, 1884	"Cancer"	?	?	Hematuria a few days after birth. Death at 2 months. No description of tumor
7	At birth	?	Kretschmer: J. Urol. **39**: 250, 1938	Malignant nephroma	0	?	Abdomen distended since birth. Tumor removed at 8 months. No recurrence
8	At birth	?	Max: Clinique, Bruxelles **8**: 705, 1893	Sarcoma	?	357 Gm.	Abdomen enlarged at birth, grew steadily. Death at 8 months
9	At birth	M	Merkel: Beitr. z. path. Anat. u. z. allg. Path. **24**: 475, 1898	Malignant nephroma	0	Bilateral: L. 850 Gm. R. 6×3.5×2.5 cm.	Abdomen enlarged since birth. Tumor removed at 6 months. Bilateral. Death 2 days later
10	4 weeks	M	Morgan: Proc. Roy. Soc. London **30**: 399, 1879	Malignant nephroma?	Subcutaneous, heart	Large	Subcutaneous metastases in skin at 4 weeks. Infant died at 9 weeks, with cardiac and subcutaneous metastases
11	At birth	F	Wentworth: Arch. Pediat. **13**: 321, 1896	Spindle cell sarcoma	0	400 Gm.	Infant lost weight since birth. Abdomen swollen at 3 weeks. Tumor weight 400 Gm.

had begun before birth it is impossible to say. It is not possible to deny that the malignant process may have been initiated before birth even in those tumors not clinically manifested before birth. Assuming the correctness of the present conception of the genesis of these tumors, one finds as a fact of possible significance the absence of benign tumors or of persistent undeveloped rests of such embryonic elements. Is one to conclude that whenever a portion of the growth zone fails to differentiate into normal renal tissue it inevitably produces a malignant tumor? In all of sections of kidneys that I have seen from routine autopsy work and other sources, only once have I encountered what appeared to be a quiescent rest of this sort. This was found in routine examination of sections from the kidney of a woman of 28 years who died from carcinoma of the ovary. The kidneys showed occasional depressed scars, apparently from healed ascending pyelonephritis, in one of which was a white nodule, 3 mm. in diameter. Microscopically, the nodule was composed of occasional tubules of columnar epithelium surrounded by smooth muscle fibers (figure). These structural elements seem to be identical with the basic elements of a Wilms tumor in which progression to malignancy has not taken place. In the literature I have failed to find mention of such rests, so they are probably rare.

Despite the frequency of embryonal nephroma in early infancy and the apparent congenital nature of the tumor in many instances, the number of cases in which such a malignant growth was demonstrated as present at birth is surprisingly small; in fact, only in 2 cases was true nephroma demonstrated as having been present at birth (Dienst; Semb), although in the other 3 cases the tumor probably was mixed nephroma not recognized as such. Several other cases repeatedly included in compilations of instances of congenital malignant renal tumor cannot be accepted as established, namely:

1. Jacobi, in 1880, reported as carcinoma of the kidney with metastases in the liver, adrenal and peritoneum in a macerated fetus what most probably was adrenal neuroblastoma.

2. Hasse was said by Kühn, in 1875, to have observed a "renal carcinoma the size of a child's head in a newborn infant," but there is no further information to establish the nature of this growth, and no published report of the case by Hasse can be found.

3. Ramdohr, in 1878, reported a case of bilateral renal tumor with many metastases, but from the account it is not possible to tell where the tumor arose or what kind it was. The illustrations indicate that probably it arose from the lower jaw and was possibly chondrosarcoma. It is a remarkable example of metastasizing malignant disease in utero, but whatever it is, it almost certainly is not a primary renal tumor.

4. Weigert, in 1876, reported as congenital bilateral renal sarcoma in a dead-born premature fetus (29.5 cm. long) what from the description and illustration was probably merely a malformation.

5. Schäffer, in 1926, reported as a mixed tumor of the single kidney of an 8 month fetus what seems to be not neoplasm but merely a congenital maldevelopment.

6. F. T. Paul, in 1886, reported finding a 7 month fetus with both kidneys symmetrically enlarged "so that they were the size of the fist of an adult man," but his description of the histologic changes as having "gone on to the development

Undeveloped nodule, resembling in structure embryonal nephroma, found in the kidney of a woman 28 years old.

of kidney structure of a normal type" does not establish this case as one of a malignant neoplasm.

There are also numerous cases reported as instances of congenital renal sarcoma in which the tumor was not demonstrated as present at birth, evidence of the presence of a tumor being first obtained at some time after birth, sometimes immediately and sometimes even after two or three years. Those tumors which seem most probably to have been

actually present as malignant neoplasms at the time of birth, as evidenced by the early symptoms or the extent of the neoplasm at a very early age, are included in table 2.

It is of course impossible to draw the line between those tumors which were probably present as malignant neoplasms at the time of birth and those in which malignancy began after birth, and there are a few recorded cases not included in the foregoing list which possibly belong there. For example:

Bankart, in 1918, reported the case of an infant observed at the fourth month with metastases in the skull, apparently from a "round cell sarcoma" of the right kidney. Death occurred at the sixth month with metastases in the right orbit, the right parietal bone and the abdominal lymph nodes. So much metastasis so early suggests antenatal malignancy, but the report is inadequate, and although it is said that the adrenals were normal, a round cell growth with metastasis to the skull suggests a neurogenic neoplasm, and Harbitz suggested that not a few of the renal tumors diagnosed as "adenosarcoma" were really neuroblastoma. A recent study by Masson has shown that these renal mixed tumors contain not only renal glandular elements, mesenchymatous elements and striated muscle but also neuroepithelial and nerve elements "which can be linked with lateral lumbar neuroepithelium and the neural crests derived from it."

Ebstein, in 1878, said that Ponfick once showed him a "round cell sarcoma the size of a man's fist" from an 18 week old child which had been restless since birth, but gave no more information.

Dr. William Hibbs has given me the data on the earliest case of nephroma recorded at the Children's Memorial Hospital of Chicago. A boy was said to have been well until the ninth week, when vomiting began. One week later he was brought to the hospital because the abdomen was bulging in all directions, rigid, and a tumor was palpable on the right side. Death occurred at 12 weeks. At necropsy the tumor was described as "double fist" in size. In about 2,200 necropsies at this institution, no malignant tumors of any kind have been definitely present at birth.

In 1926 Summer reported the case of a girl with abdomen greatly distended at 3 months, from whom a "mixed tumor" of the kidney (11 by 8 by 11.5 cm.) was removed. The child remained well at 2 years of age. The histologic description fails, however, to prove the malignant character of the growth, suggesting, rather, cystic kidney.

Ladd (1938), among his 58 cases of nephroma, had a growth in an infant but 2 months old, which very possibly had been present at birth. Dr. Farber writes me from the same hospital that in 3,000 necropsies on children there has been found no recognizable renal embryoma at

birth. In about 3,000 necropsies on premature fetuses and deadborn infants recorded in the University of Chicago and Chicago Lying-in Hospital there has never been found a renal embryoma, although several congenital cystic kidneys have been found.

ADRENAL NEUROBLASTOMA (SYMPATHETICOBLASTOMA)

Ranking in frequency much ahead of nephroma among the malignant neoplasms of early infancy is the adrenal neuroblastoma, as it was termed by Homer Wright, who first recognized it (1910), or, as Bailey recommends, the sympatheticoblastoma.[1] Redman and co-workers stated that there were about 275 cases reported in the literature to 1938, of which nearly half (113) had been reported since the review in 1933 by Scott, Oliver and Oliver. But the neurogenic adrenal malignant growth tends to appear much earlier than the nephroma; of 83 cases in the Scott, Oliver and Oliver series, 29 were observed in infants less than 6 months old. This is equally true of neuroblastoma of other parts of the sympathetic system, for in 15 such cases in this series 8 patients were under 3 years of age. Of malignant tumors that seem to be existing at birth, these tumors show by far the highest proportion, and are especially striking because of the number that have produced extensive metastases, especially in the liver, either before or soon after birth. The two reviews just cited cover so completely the general features and the bibliography of these neoplasms that nothing further need be said here on that score. The 4 malignant tumors in newborn infants observed in this laboratory are all of this type, and are briefly reported herewith.

CASE 1.—A full term girl delivered at the Chicago Lying-in Hospital, June 5, 1929, died seventeen hours after birth from atelectasis. The postmortem examination by Dr. Béla Halpert revealed in the left adrenal a nodule, about 15 mm. in diameter. Besides fetal pulmonary atelectasis, no other abnormalities were found in the body.

Microscopically, the tumor was made up of undifferentiated round cells, located in the medulla but infiltrating the cortex in places. In certain areas there was a suggestion of rosette formation. The diagnosis of neuroblastoma was corroborated by Dr. Percival Bailey. In the absence of metastases, the chief evidences of malignancy were the infiltrative character of the growth and the identity of the histologic picture with that of malignant tumors of adrenal sympatheticoblasts.

CASE 2.—A full term girl, born at the Women's and Children's Hospital by cesarean section, died Nov. 12, 1931, twenty-four hours after birth. The postmortem examination by Dr. Mercy A. Southwick revealed many developmental anomalies, namely, massive hydrocephalus, spina bifida extending from the eighth thoracic to the fifth lumbar vertebra, congenital partial coarctation of the aorta, patent ductus arteriosus with dilatation of the pulmonary artery, congenital absence of the left ureter and congenital malformation of the left second rib. The lungs were well expanded.

1. I recognize the preferability of the latter term on theoretic grounds but use the term "neuroblastoma" because of its brevity.

Nothing abnormal was noted about the adrenals in gross examination, but routine sections of one adrenal (whether left or right is not known) disclosed an abnormal area, about 2 mm. in diameter, in the medulla. Serial sections showed this small growth to be infiltrating the adjacent cortex. It was composed of small, undifferentiated round cells, each consisting chiefly of a large nucleus, slightly vesicular, with a distinct nucleolus. No evidence of rosettes or fibrils was found, presumably because of the lack of maturity and differentiation of the cells. The appearance was quite typical of the most malignant type of adrenal neuroblastoma. Sections of the other adrenal and other viscera revealed no similar abnormality.

Case 3.—A boy was born to a 25 year old primipara, Dec. 25, 1936, at the South Shore Hospital. Although, according to the calculated data, the infant was full term, it weighed but 4 pounds (1,815 Gm.), although 45 cm. in length, and was poorly nourished and of poor color. The placenta was very small, about half the size of that of a normal full term pregnancy, and contained a large marginal infarct. Presumably the infant was somewhat premature. No obstetric or family history of significance was elicited. The infant was placed in an incubator, and although it cried and breathed well at first, after twenty-four hours it became dyspneic and cyanotic, and died.

Postmortem examination by Dr. John P. Fox revealed partial atelectasis of the right lung with early bronchopneumonia, acute cardiac dilatation with marked generalized acute passive congestion, persistent omphalomesenteric duct, a cyst in the thymus, congenital vascular anomalies in the brain and a neuroblastoma of the right adrenal.

The following description of the adrenals is from the necropsy protocol: "The adrenals are, as is usual at this age, disproportionately large. The left is of normal shape and appearance on the cut surface, and is estimated to weigh about 2 Gm. The right, however, contains a large firm nodule in the upper portion, which measures about 1.5 by 2 by 1 cm. in its various diameters. The weight of the gland as a whole is estimated to be 4 Gm. On the cut surface the lower portion of the gland is normal, but in the upper portion the yellow cortex expands widely to enclose on all sides a brownish red, sharply circumscribed nodule of the dimensions already indicated."

The microscopic observations were reported as follows: "In the right adrenal the cortex is essentially normal and contains practically no lipoid. The entire medullary area is replaced by a neoplasm, which consists of round cells with hyperchromatic nuclei, some of which are in typical rosette formation, and in the more diffuse areas delicate fibrillae extend in all directions between the cells. The stroma is extremely vascular and hemorrhagic, particularly at the border, which is not sharply circumscribed from the cortex; but the tumor cells do not conspicuously permeate the cortex, although there is a general marginal invasive tendency. The left adrenal shows nothing unusual."

The brain was studied in the division of neurology by Dr. Percival Bailey, whose report follows: "The striking pathologic feature is the anomaly of the cerebral veins. The middle cerebral veins have fusiform enlargements at various intervals on the left side. As the vein passes over the insula, one of these enlargements measures 5 mm. in diameter. The left rolandic vein is 2 mm. in diameter just before it enters the sinus. The right middle cerebral vein as it enters the sylvian fissure is about 1 mm. in diameter, but its first tributary, lying in the inferior temporal sulcus, has a diameter of 4 mm. There is a mass of veins

overlying the insula of the right sylvian fissure having an average diameter of 3 mm. The right rolandic vein is represented by a thin band of a diameter of about 0.5 mm. There are dilated veins in both parieto-occipital notches, over the right frontal and right occipital poles. The arteries of the base of the brain are of normal size. Over the posterolateral border of the right half of the cerebellum is an enormous venous sinus, 5 mm. in its greatest diameter. There are smaller veins in a similar position on the left hemisphere. Sectioning of the brain reveals no dilatation of the internal venous plexuses. Impression: congenital vascular anomalies of the brain."

The other developmental anomaly was a small cyst in the thymus, which was described as follows: "The thymus is normal except for hemorrhage into the parenchyma. Between the lobules is an irregular cystlike space lined by cuboid cells resting on a dense fibrous base. These cells resemble unflattened mesothelium. In the wall are a group of trabeculae of osteoid tissue, part of which is calcified. There is hemopoietic tissue around these trabeculae."

CASE 4.—This, by far the most remarkable example of prenatal malignancy of which I can find record, was examined by Dr. Edith Potter. Because of its unusual character and significance, the case will be the subject of a special report by Dr. Potter, who permits me to present the following brief summary of the salient features: A white male fetus, weighing 1,385 Gm., 37.5 cm. long and presumably at about the eighth month of development, died before delivery. Craniotomy was performed and the skull contents removed by saline irrigation, and therefore, unfortunately, nothing is known about the conditions within the brain. The rest of the body presented a most remarkable aggregation of neurogenic tumors, the largest of which was a pair of bilateral masses, each about 6 by 4 by 4 cm., lying between and involving the adrenals, compressing but not involving the kidneys, and connected with each other by another tumor mass. This tumor in large part resembled an undifferentiated neuroblastoma with areas of necrosis and calcification, but there were also nerve fibers and ganglion cells in varying degrees of maturity. The liver contained what seemed to be metastases of the neuroblastic elements. The sympathetic ganglions were generally involved in tumor formation with the same three elements, neuroblastomatous elements, ganglion cells and nerve sheath tumors. The vagus was greatly enlarged by ganglioneuromatous growth, and the wall of the urinary bladder contained a tumor mass, also composed of ganglion cells and hyperplastic nerve bundles. Although the adrenals were involved, most of the cortical tissue had been preserved, and this tumor may be looked on as one arising from extra-adrenal sympathetic elements. The nerves of the cerebrospinal system also were enlarged through proliferation of the Schwann cells.

These 4 tumors have been encountered in approximately 3,000 necropsies on deadborn fetuses or newborn infants. It is most probable that more careful examination of fetal adrenals would bring to light occasional early lesions of this sort, especially of the type described in case 2, in which the abnormal tissue was not seen in the gross examination of the adrenal and was found only in routine microscopic examination. In fact, the question may properly be raised as to whether this should be looked on as actually a malignant growth or as merely an abnormally large accumulation of undifferentiated sympatheticoblasts.

Perhaps such accumulations may be present not rarely during fetal life and either retrogress or mature into normal tissue elements. They may be like the collections of undifferentiated cells described in fetal brains by Amolsch, by Ostertag and by Tuthill, in fetal retinas by Seefelder and by Ginsberg and in chicken embryos by von Szily. Probably the small collection of cells observed by Canavan and Hemsath in the floor of the fourth ventricle of a nearly full term fetus, "about 80 cells in the section," represents something of this sort, although this case was reported as one of glioma.

That neuroblastomatous cells, even when malignant in character, may go on to differentiate into mature types of cells of nonmalignant character is demonstrated by the case reported by Cushing and Wolbach in which a typical malignant neuroblastoma observed in a 2 year old boy was found ten years later to have become completely differentiated into ganglion, capsular and neurilemma cells. This capacity for differentiation may explain the fact that malignant adrenal neuroblastoma is seen almost entirely in young infants, on the assumption that if the abnormal aggregations of such cells produced occasionally during early developmental stages do not soon acquire malignant characters they go on to maturation, or else disintegrate and disappear. Support for this view is given in a case reported by Martius, in which some of the tumors were frankly malignant neuroblastoma of the cervical sympathetic system but one was benign ganglioneuroma. Wahl reported the case of a 2½ year old girl who in addition to metastasizing neuroblastoma of the adrenal had also ganglioneuroma and paraganglioma of the adrenal and hyperplasia of the sympathetic ganglions. Wahl and Craig also reported ganglioneuroma, metastasizing neuroblastoma and ganglioneuroblastoma in a 28 year old Negro, and the mixed renal neoplasm observed by Potter in this laboratory presents everything from malignant metastasizing neuroblastoma to mature ganglioneuroma and neurinoma of mature sheath cells ("schwannoma"). Quirin even reported a case in which after removal of metastases the patient recovered, which, in his opinion, was because the primary tumor and other metastases progressed to mature benign ganglioneuroma. [Unfortunately this important observation cannot be verified, as the abstracter failed to cite the original publication, which cannot be located.]

A remarkable confirmation of the conception of congenital malignant neuroblastoma as a neoplasm capable of maturation and change to a benign growth, or perhaps of disappearing altogether, is furnished by Drs. Sidney Farber and Thomas H. Lanman of the Children's Hospital, Boston. They have written me that they have had in that institution young infants, one 6 days old and the others in the early months of life, in whom large tumors were present that were proved micro-

scopically to be neuroblastoma; yet all these infants are alive and well some time later. In 1 case a biopsy was made on a metastatic nodule in the liver, but the child is living and well one and one-half years later.[2]

Further support to this view is the fact that some of the tumors that are unquestionably malignant adrenal neuroblastoma do contain more differentiated nerve cells. For example, in the case reported by Glomset of a 2 year old boy with a malignant tumor of the right adrenal which had produced widespread metastases, although most of the tissue was of undifferentiated neuroblastic elements, in some parts recognizable ganglion cells were present. This was very evident in the Potter case cited previously. In the case reported by Jean Smith, in which subcutaneous metastases were present at birth but with survival of the infant until the age of 19 months, the well circumscribed tumor in the adrenal contained "ganglion cells in addition to numerous nerve bundles." Metastases were also present in the pancreas and abdominal lymph nodes, indicating that the tumor was truly malignant despite its histologic appearance. These observations suggest that this tumor was originally a malignant neuroblastoma in which some parts had matured, as in the case reported by Cushing and Wolbach, while others remained malignant. Similar are the cases reported by Dunn, by Blacklock and by others of adrenal neuroblastoma with mature ganglion cells and immature neuroblasts in the primary growth, but in the metastases only the immature cells. Particularly striking is a case recently studied in this laboratory in which a boy of 9½ years had a tumor diagnosed as benign ganglioneuroma in one adrenal, cutaneous café au lait spots and a malignant tumor somewhat resembling neuroblastoma in the brain. Stern and Newns also reported a tumor of a sympathetic ganglion which, although it contained many well formed ganglion cells, was malignant enough to invade the kidney. They stated that nearly always tumors of this type contain cells in different stages of development; "in some parts a very immature type of cell and in others a more differentiated type of cell predominates." As completely benign ganglioneuroma has also been reported in young children, it is probable that the abnormal neuroblastic elements may mature either in whole or in part, to produce tumors of varying degrees of malignancy. Rarely, benign ganglioneuroma may be found in the adrenal itself (see review by Wassmund).

2. E. P. Lehman reported a case in which a tumor described as typical adrenal neuroblastoma was removed surgically from a child 11 months of age (J. M. Research **36**:309, 1917); later he reported that the child was still in perfect health after fifteen years (Ann. Surg. **95**:473, 1932). In this case no evidence of metastasis was noted, although enlargement of a cervical node had been present since the nineteenth day of life but was regressing at the time of operation, so that its neoplastic nature was doubted.

The case reported by Miller as an instance of ganglioneuroma of the retroperitoneal sympathicus nerve with metastases in regional lymph nodes raises the question whether this may not have been originally malignant neuroblastoma, becoming benign even after local metastasis had occurred.

It is possible that retinal neuroblastoma exhibits this capacity for spontaneous loss of malignancy to a less marked degree. Sattler, in 1926, stated that very rarely cases had been reported in which it seemed certain that malignant retinoblastoma in a child had spontaneously ceased to grow. He cited cases reported by Siegrist, Meller and Axenfeld in which after one eye had been removed because of a growth proved microscopically to be malignant retinoblastoma, a small tumor in the retina of the other eye had ceased to grow and gradually regressed; in 2 cases the observations had been made over a period of ten years. Even more striking is the case of De Kleijn, for here the second eye became blind, was enucleated five years later and was found to contain only necrotic and calcified tissue—presumably, but not certainly, necrotic retinoblastoma. Although absolute proof of the malignant character of these growths is necessarily lacking, the ophthalmoscopic evidence of the tumor in a child with malignant retinoblastoma in the other eye leaves little room for doubt. Also in a retinoblastomatous family with 3 members whose lesions were fatal, reported by Purtscher, there were 2, a 4 year old boy and his 29 year old aunt, who showed ophthalmoscopically what appeared to be retrogressing retinal tumors. Less significant are the 3 cases cited by Sattler of cessation of growth of gliomatous tumors in eyes attacked by suppuration.

Levin pointed out that in some adults with glioma (transitional glioma, Globus) there seems to be "an unconsummated transition of the undifferentiated and therefore malignant forms of gliomatous tumor into the more differentiated and essentially benign types."

Tumors arising from the peripheral nerves do not behave this way, for in 143 cases of neurogenic sarcoma considered by Stewart and Copeland only 1 tumor was in an infant, and only 1 other was in childhood.[3]

The cases of neuroblastoma of the adrenals that are definitely proved, those that are probably, and those that are possibly, true cases of congenitally malignant adrenal neuroblastoma are summarized in tables 3, 4 and 5, respectively.

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3. This case is cited by Stewart and Copeland as reported by McGlannan. The patient, a girl, is described by them as having present in the ischiorectal region at birth a myxosarcoma. This was partly excised at 3 months, and death followed shortly after. The original article, however, reports this tumor as teratoma with sarcomatous development, and not evidently a neurogenic tumor.

Of the 55 cases reviewed in tables 3, 4 and 5, in no less than 16 both adrenals were involved. In some of these, especially the cases of Capon and of Orr, the tumors were in all probability metastases, but whether this is true of all the cases is not readily determined.[4] For example, in Bergström's case the tumors were the same size in each adrenal, and although there were subcutaneous, renal and splenic metastases, there were no metastases in the liver. This bilateral occurrence is so frequent that the question has been raised whether the so-called metastases, including even those in the liver, are really metastases at all, rather than multicentric development from numerous foci of sympathogonia. For example, Giordano found in a deadborn infant nodules of sympathogonia in both adrenals and in the liver. But the widespread invasion of the liver in so many cases makes it difficult to consider the condition as other than metastasis. On the other hand, there have even been a few authors who have reported cases in which they interpreted the hepatic lesions as primary neuroblastoma. Jungmichel reported that in a 5 week old infant with a liver so full of neuroblastic tumor nodules that the organ weighed 1,255 Gm., microscopic examination of both adrenals gave no evidence of any tumor formation that could have been derived from the sympathetic nervous system, although one adrenal was enlarged because of hemorrhage, and he found no primary tumor outside the liver.

Dietrich and Siegmund said that they had observed, as have others, that when neuroblastoma arises in one adrenal, although the other adrenal may be grossly normal, there may be found in it collections of undifferentiated sympathogonia balls which, according to site and appearance, are certainly not metastases. In this apparently normal adrenal it may also be observed that the differentiation of mature medullary elements is much less than normal, although the other portions of the sympathetic system are not abnormal. In the Potter case the primary tumor was probably in extra-adrenal sympathetic tissues, and the small areas in the liver and adrenals might have been either multicentric primary foci or metastases.

Stern and Newns pointed out that neuroblastoma sometimes arises from the abdominal sympathetic chain rather than from the adrenals. Four of their 25 cases of tumor of the sympathetic nervous system in childhood were of this sort, without adrenal involvement, and in 1 case the growth arose in the intrathoracic sympathetic chain. In many cases therefore neuroblastoma has been mistaken for lymphosarcoma, and reported as such in the earlier literature.

4. It may be of some significance that the only case of congenital *benign* tumor of the adrenal that I can find was one of bilateral cortical adenoma in a 4 day old boy, reported by Warthin.

TABLE 3.—*Neuroblastoma of Adrenal Definitely Present at Birth*

No.	Age at Death	Sex	Author	Adrenal Involved	Metastases	Size of Adrenal Tumor	Comment
1	3 weeks	F	Askin and Geschickter: J. Pediat. **7**: 157, 1935	L	Liver, right adrenal	.....	Symptoms since birth; enlargement of abdomen since 1 week (author's case 10 A&G)
2	31 days	F	Bergstrom: Am. J. Clin. Path. **7**: 467, 1937	Both	Skin, choroid plexus, spleen, skull, kidneys, dura	6×3.5×3 cm. each	Many metastases in skin at birth; innumerable at death on 31st day. Cells primitive
3	6 weeks	M	Dalton: Tr. Path. Soc. London **36**: 247, 1885	L	Liver	Hen's egg	Abdomen swollen from birth. Liver 37½ ounces (1,063 Gm.). Reported, and often listed as sarcoma
4	At term	M	Giordano: Arch. ital. di pediat. **5**: 148, 1937	L	Liver	5.1×4.0×3.2 cm.	Externally normal liver and right adrenal contained microscopic tumor nodules or foci of undifferentiated sympathogonia
5	At term	?	Hagstrom: Am. J. Obst. & Gynec. **19**: 673, 1930	R	Liver	6×6×5 cm.	Liver weighed 700 Gm. Dystocia. Embryotomy. This is case 14 of Askin and Geschickter report; path. report by E. Smith
6	36 hr.	F	Landau: Frankfurt. Ztschr. f. Path. **11**: 26, 1912	Both, espec. L	Liver, right adrenal?	3.4×3.2×2.2 cm.	Abdomen distended at birth. Liver greatly enlarged, causing rupture of splenic vessels
7	4 hr.	M	Makai: Pest. med.-chir. Presse **43**: 486, 1907	?	Yes	5×3×3 cm.	Says metastases present but does not say where, although cited in literature as skull metastases. Called adenosarcoma
8	2 weeks	M	Richards: Guy's Hosp. Rep. **59**: 217, 1905	L	Liver	2×1.5 inch (5×3.8 cm.)	Abdomen large at birth. Liver weight 1,850 Gm. Called "small round cell sarcoma with rosettes"
9	7 weeks	M	Rinscheid: Virchows Arch. f. path. Anat. **297**: 508, 1936	R	Liver, lymph nodes, kidney, subcutaneous	About size of heart	Metastasis on neck at birth. Neuroblastomatous fibrils
10	9 days	..	Roman: Bull. Buffalo Gen. Hosp. **4**: 58, 1926	Both	Liver	L 15 Gm. R 3 Gm.	Liver almost replaced: weight 765 Gm. Jaundice from birth. Not certain whether growth in right adrenal was metastasis
11	3 weeks	F	Saphir: Arch. Path. **4**: 207, 1927	L	Liver	4×6 cm.	Skin white since birth. Abdomen enlarged gradually. Liver weight 650 Gm. Undifferentiated cells
12	18 days	M	Spreng: Schweiz. med. Wchnschr. **66**: 1192, 1936	L	Liver, subcutaneous, adrenal bladder	6×4.5×3.5 cm.	Subcutaneous nodules at birth. Liver 580 Gm. Death from rupture of hepatic metastasis
13	6 weeks	F	van Veen: Jahrb. f. Kinderh. **122**: 214, 1928	R	Liver, right kidney	About size of kidney	Abdomen swollen from birth and progresively enlarging. Liver filled abdomen
14	At term	F	Wells and Halpert: To be published	L	0	15 mm.	Infiltrative growth, typical histologically

TABLE 3.—*Neuroblastoma of Adrenal Definitely Present at Birth—Continued*

No.	Age at Death	Sex	Author	Adrenal Involved	Metastases	Size of Adrenal Tumor	Comment
15	24 hr.	F	Wells and Southwick: To be published	?	0	2 mm.	Found on routine microscopic examination of adrenals. Many developmental abnormalities, including spina bifida
16	24 hr.	M	Wells and Fox: To be published	R	0	1.5×2×1 cm.	Typical rosette formation and peripheral invasion. Congenital vascular anomalies in brain
17	Stillborn	M	Wright: J. Exper. Med. 12: 550, 1910	Both	Meninges	R 3×2×2 cm. L smaller	Dr. Haythorn writes me that there were about 30 metastases up to 4 mm. in diameter in the meninges

CONGENITAL NEUROGENIC TUMORS ARISING OUTSIDE THE ADRENALS

Against the view that the numerous tumor nodules found in the liver and elsewhere in cases of adrenal neuroblastoma represent multicentric primary malignant growth is the fact that the neural elements outside the adrenals so seldom produce congenital malignant tumors. All the case reports found that seem to deal possibly with congenital extra-adrenal malignant tumors of nerve tissues are given in table 6.

In addition to these there have been several tumors diagnosed as sarcoma and mentioned in the lists of sarcoma, as well as tumors of undetermined type, which possibly were neuroblastoma that was erroneously diagnosed (table 8, cases 5 and 6; table 9, cases 4, 13, 17, 25 and 33; table 11, cases 4, 6 and 8).

In congenital teratoma, areas histologically resembling neuroblastoma have been described but without adequate evidence that they were really malignant tissues rather than masses of undifferentiated fetal neurogenic tissues such as commonly abound in teratoma.

1. Harbitz reported a remarkable case of a 4 month fetus, only 17 cm. long, with a proportionally huge sacral tumor, 7.25 by 6.5 by 3.5 cm., which contained microscopically masses of undifferentiated nerve tissue with rosette formation, associated with embryonic cartilage. Although Harbitz considered this neuroblastoma, it is impossible to be sure that the undifferentiated character of the neurogenic tissues may not have depended on the early stage of fetal development rather than on true malignancy. Perhaps, had the fetus gone on to full term, the undifferentiated neural elements would have progressed to maturity and the teratoma been considered benign.

2. Bode observed in an 8 month fetus a retroperitoneal tumor "as large as an infant's head," so large that it caused dystocia, which tumor he described as gliosarcoma, containing also cartilage and bone, supposedly derived from the sympathetic nerve tissues. Only a brief abstract of a report at a society meeting seems to have been published; so a critical consideration is not possible.

3 and 4. Mallory diagnosed as glioma a tumor of the buttock, present since birth, which was removed at 14 weeks, without recurrence, and reported by

TABLE 4.—*Probably Congenital Malignant Adrenal Neuroblastoma*

No.	Age When Noticed	Age at Death	Sex	Author	Adrenal Involved	Metastases	Size	Comment
1	7 weeks	2 months	F	Amberg: Arch. Pediat. **21**: 582, 1904	Both?	Liver, 1,200 Gm.	±40 Gm.	Right adrenal only microscopic involvement, perhaps metastatic. Patient one of twins
2	?	2 months	M	Askin and Geschickter: J. Pediat. **7**: 157, 1935	L	Liver	4 cm.	Negro infant. Liver wt. 870 Gm. Death from meningitis
3	?	6 weeks	F	Capon: J. Path. & Bact. **31**: 659, 1928	Both?	Liver, subcutaneous adrenal?	.....	Not stated when first seen. Liver wt. 18 oz. (510 Gm.). Many subcutaneous metastases. Many nodules in both adrenals
4	3 weeks	3 weeks	M	Johan: Jahrb. f. Kinderh. **97**: 200, 1922	R	Liver	?	Abdomen greatly enlarged at 3 weeks. Liver extensively invaded. Tumor diagnosed as lymphosarcoma of liver because fibrils not demonstrated
5	8 weeks	10 weeks	..	Lewis and Geschickter: Arch. Surg. **28**: 16, 1934	?	Liver	?	Abdomen swollen. Patient jaundiced
6	12 days	6 weeks	M	Matzdorf: Virchows Arch. f. path. Anat. **266**: 416, 1928	L	Liver	.....	Abdomen swelling since 12 days. Entire liver infiltrated
7	4 weeks	6.5 weeks	F	Pepper: Am. J. M. Sc. **71**: 287, 1901	R	Liver	"Walnut"	Abdomen much swollen at 4th week. Liver wt. 2¼ lb. (1,132.5 Gm.). Reported as congenital sarcoma of liver
8	3 days	5 weeks	F	Rostkowski: Pedjat. polska **12**: 248, 1932; abstracted, Zentralbl. f. Kinderh. **27**: 575, 1933	L	Subcutaneous	.....	Original article not available. Tumor reported as round cell sarcoma of adrenal. Twin brother normal. Subcutaneous nodules noted on 3d day
9	Birth	10 days	?	de Ruyter: Arch. f. klin. Chir. **40**: 98, 1890	L or both	Liver, right adrenal?	"Apple"	Reported as lymphosarcoma of adrenals with metastases in liver (Israel's diagnosis). Liver 20 × 12.5 × 6.5 cm. Right adrenal half the size of the left
10	?	10 weeks	..	Scott, Oliver and Oliver: Am. J. Cancer **17**: 396, 1933	Both	Liver	.....	Liver nearly filled abdomen
11	4 days	8 days	F	Shukowsky: Jahrb. f. Kinderh. **69**: 213, 1910	L	None	"Hen egg"	Tumor grew rapidly. No metastases described. Called sarcoma. Death as result of hemorrhage from tumor
12	Birth	2 weeks	?	Smirnowa-Zamkowa: Ztschr. f. Krebsforsch. **22**: 218, 1925	R	Liver, 450 Gm.	"Walnut"	Reported as "gemischte embryonale Geschwulst" of kidney, but the description of tumor as located above right kidney, separated from it by a capsule, the type of liver involvement, and the histologic details leave no doubt that this was an adrenal neuroblastoma
13	3 weeks	7 weeks	F	Wilke: Jahrb. f. Kinderh. **70**: 209, 1909	L	Liver, 1,245 Gm.	7 × 4.5 × 5	Abdominal swelling noted at 3 weeks. Reported as round cell sarcoma primary in liver and adrenal
14	3 weeks	3 weeks	?	Wollstein: Surg., Gynec. & Obst. **46**: 774, 1928	..	Liver	.....	Enlarged abdomen noted at 3d week. Liver wt. 390 Gm.
15	Birth	1 mo.	M	Zamorani: Riv. di clin. pediat. **25**: 456, 1927	R	Liver, subcutaneous	.....	Reported as lymphosarcoma of liver. Probably adrenal neuroblastoma

15	Birth	1 mo.	M	Zamorani: Riv. di clin. pediat. **25**: 456, 1927	R	Liver, subcutaneous	Reported as lymphosarcoma of liver. Probably adrenal neuroblastoma

TABLE 5.—*Possibly Congenital Adrenal Neuroblastoma*

No.	Age When First Noticed	Age at Death	Sex	Author	Adrenal Involved	Metastases	Size	Comment
1	3.5 mo.	4 mo.	M	Carmichael and Wade: Lancet **1**: 1217, 1907	?	Liver, frontal bone	No mention	Reported as sarcoma of liver, with no mention of adrenal, but metastasis in skull and character of hepatic growth suggest adrenal neuroblastoma
2	Early	3 mo.	?	Farre: The Morbid Anatomy of the Liver, London, Hurst, Reese [and others], 1810	L	Liver, lungs	Large	Reported in 1810 as cancer of liver and retroperitoneal glands. May be lymphosarcoma but more probably neuroblastoma. Large mass about left kidney resembling "putrid brain"
3	.....	35 days	F	Fujimori, cited by Nakatani: Tr. Soc. Path. Jap. **24**: 581, 1934	..	.....	.....	
4	Birth	8 weeks	?	Heaton: Lancet **1**: 645, 1893.....	R	Liver, weight 49 oz. (1,389 Gm.)	"Small"	Reported and often cited as small round cell sarcoma of liver with metastasis to adrenal, but probably adrenal neuroblastoma
5	2 mo.	16 mo.	M	Hertz and Secher: Hospitalstid. **60**: 1093, 1917	..	Liver	.....	After 6 mo. Addison's disease present. Did not grow rapidly until 13th month. Doubtful as to congenital malignancy
6	.....	14 weeks	..	Hewlett: Intercolon. M. J. Australasia **4**: 615, 1899; abstracted, Lancet **1**: 427, 1900	..	Liver, lungs	.....	Although the author says no other organs were affected, it seems probable that an adrenal tumor was overlooked
7	?	6 weeks	M	Herxheimer: Beitr. z. path. Anat. u. z. allg. Path. **57**: 112, 1913	R	Liver, duodenum, lymph nodes	"Large walnut"	No information as to clinical history
8	?	6 weeks	?	Holt and Howland: Diseases of Infancy and Childhood, ed. 10, New York, D. Appleton-Century Company, 1933, p. 333	..	Liver	.....	Merely mention seeing such a tumor, no details
9	.....	14 weeks	..	Lapointe and Lecène: Arch. de méd. exper. et d'anat. path. **19**: 69, 1907	L	Liver	"Nut"	Liver very large
10	8 weeks	9 weeks	F	Lesné and others: Arch. de méd. d. enf. **30**: 133, 1927	Both	Liver	.....	Abdomen distended at 2 mo. Patient died 1 week later. Liver weight 1440 Gm.

TABLE 5. *(Continued)—Possibly Congenital Adrenal Neuroblastoma*

11	?	16 weeks	F	Meisenbach: Weekly M. Rev. **9**: 433, 1884	..	Liver	.....	Liver filled entire abdominal cavity, mottled "like red castile soap." No mention of adrenals. Reported as myxosarcoma of liver, but may be secondary neuroblastoma
12	.....	2 mo.	M	Mittelbach and Szekely: Frankfurt. Ztschr. f. Path. **47**: 517, 1935	L	Liver? Adrenal?	2.2 cm.	Associated with many malformations. Small cell collections in other adrenal and liver. Liver not enlarged
13	?	3 mo.	M	Nakatani: Tr. Soc. path. jap. **24**: 581, 1934	L	.....	.....	
14	.....	69 days	M	Nakatani: Tr. Soc. path. jap. **24**: 581, 1934	L	.....	.....	
15	.....	105 days	F	Nakatani: Tr. Soc. path. jap. **24**: 581, 1934	Both	.....	.....	
16	Dead-born	Fetus 7 mo.	F	Nyhoff: Zentralbl. f. Gynäk. **35**: 808, 1911	L	No	"Half fist"	Reported as sarcoma "perhaps from left kidney or adrenal," adherent to pancreas and intestines
17	5 weeks	4 mo.	F	Orr: Edinburgh M. J. **8**: 221, 1900.....	R	Liver, left adrenal	+6 oz. (170 Gm.)	Reported as round cell sarcoma of adrenals. Liver weight 3 pounds (1306.5 Gm.). Left adrenal studded with tumor nodules. Histologic appearance of typical neuroblastoma
18	7 weeks	8 mo.	M	Packard: Univ. M. Mag. **3**: 387, 1891.....	Both?	Mediastinal, subcutaneous, liver, pleura	"Walnut"	Reported as congenital lymphosarcoma with metastases to adrenals, but may well be adrenal neuroblastoma
19	3 weeks	5 weeks	?	Parker: Tr. Path. Soc. London **31**: 290, 1880	?	Liver	Orange?	Reported as round cell sarcoma of liver. No mention of adrenals but left kidney and spleen were connected by a mass of tumor the size of a tangerine orange. Liver weight 32 oz. (907 Gm.), infiltrated extensively
20	Birth	19 mo.	..	Smith: Lancet **2**: 1214, 1932.....	R	Subcutaneous, abdominal glands, pancreas	"Golf ball"	Cutaneous nodules present since birth. Contained mature ganglion cells, but adrenal and other tumors were medullary neuroblastoma
21	.....	3 mo.	?	Stern and Newns: Arch. Dis. Childhood **12**: 267, 1937	Both	Liver lungs, skull	.....	

TABLE 6.—*Extra-Adrenal Congenital Malignant Neoplasms of Nerve Tissue*

No.	Age When First Observed	Age at Death	Sex	Author	Location	Metastases	Comment
1	Birth	Birth	?	Amolsch: Am. J. Clin. Path. **5**: 371, 1935...	Brain	No	Tumorous growth of large cells, "glioblastoma," causing hemorrhage in thalamic region at birth
2	14 weeks	?	?	Braune: Arch. f. Kinderh. **112**: 193, 1937...	Brain	No	Sudden onset at 14 weeks. Large glioma of left hemisphere
3	Birth	Birth	M	Fischer: Frankfurt. Ztschr. f. Path. **28**: 603, 1922	Left cervical sympathetic nerve	No	Tumor size of "hazelnut" in left side of neck. Immature ganglioneuroma with immature cells, rosette formation, but also mature ganglion cells
4	Birth	36 hours	?	Leicher: Thesis, Munich, 1937.....	Right cervical sympathetic nerve	No	"Walnut-sized" tumor in right cervical plexus near upper thoracic aperture. Small immature cells, no rosettes
5	14 weeks	16 weeks	F	Landrop: Hospitalstid. **1**: 8, 1893.....	Posterior mediastinum	Liver	Walnut-sized tumor right side 5th dorsal vertebra. Liver full of metastases (1,625 Gm.). Reported as round cell sarcoma of liver, but report suggests neuroblastoma. As adrenals were normal, possibly retroperitoneal origin
6	Birth	8 mo. fetus	M	Potter: To be published.....	Between adrenals	Liver, adrenals?	Two large masses (6 × 4 × 4 cm.) between the adrenals, connected by a similar mass of mixed neuroblastomatous, ganglioneuromatous and nerve elements. Small tumor areas in adrenals may be extension of metastasis, less likely primary
7	Birth	Full term	F	Russell and Ellis: Arch. Dis. Childhood **8**: 329, 1933	Brain	No	Described as polar spongioblastoma of left cerebral hemisphere, 8.5 × 7.5 × 6 cm.
8	.....	7 days	F	Schilder: Frankfurt. Ztschr. f. Path. **3**: 317, 1909	Abdominal sympathetic nerve	No	Arore in sympathetic nerve mesial to right kidney and contained malignant neuroblasts infiltrating and destroying ganglion cells. Size 13 × 7 × 5 mm.
9	1 month	1 month	F	Schultz, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1926, vol. 8, p. 757	Left abdominal sympathetic nerve	No	Tumor 4 × 3.5 × 2 cm. Typical malignant histologic appearance, with rosettes. Spina bifida. Bronchopneumonia. No clinical evidence of tumor
10	2 weeks	8 weeks	M	Wollstein and Bartlett: Am. J. Dis. Child. **25**: 257, 1923	Brain	No	"Glioma sarcomatodes" of left cerebral hemisphere, which grew rapidly and ruptured through frontal bone and scalp

Kimpton. Another tumor of the buttock is described by the same author as "ependymal glioma with cystic dilatation," but the malignant character of these teratomatous growths is not established by the evidence presented.

CONGENITAL MALIGNANT TUMORS OF THE LIVER

Primary malignant tumors of the liver are rare, at least among Caucasians. A surprisingly large proportion of them are found in young persons. Steiner, in 1938, found in the literature reports of 105 cases of primary carcinoma of the liver in children under 16 years of age, "of which 75 have presented definite evidence justifying the diagnosis." It is to be noted that the 3 cases of carcinoma in early infancy included in Steiner's list and in all other compilations as presumably congenital were all reported so long ago that the diagnosis made at that time is entitled only to skepticism, namely: Nöggerath (1854), Widerhöfer (1859), Gee (1871). It is difficult to believe that these were really cases of carcinoma of the liver when the vastly greater necropsy material of recent years has yielded no cases. These 3 cases have been so consistently cited in the literature as proved cases of congenital carcinoma of the liver that the evidence should be carefully weighed. The original reports gave information as follows:

1. Nöggerath. The nature of the case is indicated in the title: "Geburtshinderniss in Folge eines Lebercarcinoms beim Neugeborenen." ("Difficult Birth in Consequence of a Liver Carcinoma in a Newborn Infant.") A full term girl was born dead, with a greatly swollen abdomen. The liver weighed 2¼ *Pfund*, (probably about 1,050 Gm.), was uniformly enlarged, mottled and full of firm nodules. Microscopically, the individual growth consisted of a loose mass of cells, each three times the size of a red cell. The other organs were normal although nothing is specifically said about the adrenals, which it is known often escaped observation in necropsies even much more recent than 1854. As to the cause, it is suggested that the shock the mother received when a mouse ran across her foot may have had something to do with it. Certainly the information contained in this article is far less than enough to prove that this is a primary carcinoma of the liver so large as to cause dystocia, especially as no one in more recent years has ever seen such a condition.

2. Widerhöfer. A newborn girl died from peritonitis, attributed to volvulus, on the third day. "From the lower border of the left lobe of the liver grew a very delicate network structure, which contained also areas of bony hardness." This growth was continuous with that strangling the intestines. No mention is made of metastases or of tumors in any organ. Both Wedl and Schott diagnosed this growth as *Gallertkrebs* (colloid cancer). In his résumé, however, Widerhöfer said, "The cellular tissue strings could be the product only of an intrauterine peritonitis." In this report I can see no convincing evidence that the tumor was carcinoma, and if it really was a *Gallertkrebs*, that would be evidence that it was not primary in the liver. I have no good idea what the condition was, but suspect some developmental abnormality or teratoma leading to intestinal observation.

3. Gee. A boy who died at 5 months had a tumor the size of a hen's egg, first noticed at 4 months. This had grown rapidly and at necropsy the liver weighed 40½ ounces (normal weight, 7 to 8 ounces) (1,205 Gm. [normal weight, 198.5 to 227 Gm.]), being studded with white tumor nodules up to the size of a "peeled walnut," in all lobes. No growths were found in other parts of the body. The tumor nodules were of fibrous character grossly, and microscopically "consist of a dense fibrillated stroma with small meshes, which are packed full of small cells." The multicentric distribution of fibrous nodules does not correspond to the diagnosis of "primary carcinoma of the liver." Neither is there any evidence that the process was congenital, since it was first noticed at 4 months.

Other cases often found referred to as examples of congenital carcinoma of the liver are the following:

Hofmann, in 1866, reported as an instance of "cancer of the liver, pancreas and mesenteric glands in the newborn" the case of an infant born at the eighth month of gestation, who lived only one-half hour. The liver showed deep in the left lobe a "cartilage-like scar, three lines thick"; the pancreas also was hard, and the mesenteric nodes were enlarged. Wedl, who seems to have been inclined to call many things cancer, called these lesions "cancerous infiltration," which seems highly improbable. As the mother said that all her pregnancies had terminated in miscarriages, it seems probable that the lesions were those of congenital syphilis.

Many reviewers have mentioned that Leichtenstern referred to a case reported by Siebold of cancer of the liver in the newborn. On examining Siebold's paper (1854) I find that he merely cited Nöggerath's case, which has been discussed (p. 556).

Another case often mentioned as one of congenital cancer of the liver, reported by Samuel Gross in 1857, concerns a Negro boy who died at 3 months, the liver containing many hard nodules, in size "from a shot to a three cent piece." Gross called it a "scirrhus." From the description it may well have been infantile cirrhosis with nodular regenerative hyperplasia. That the finding was a malignant neoplasm is highly improbable.

Coming to later times, I find reported as primary carcinoma of the liver a tumor observed by Dansie in a male infant. As the first symptom, abdominal distention, was not observed until the eighth week, the congenital nature of the malignant process is not established, but at death in the seventeenth week the liver weighed 2 pounds 3¼ ounces (996 Gm.), so the tumor very probably had been present since birth. The liver was mottled with purplish areas up to ¼ inch in diameter; extrahepatic tumors were found, and there was no jaundice. Microscopically, there were "groups of normal liver cells amongst masses of polymorphous tumor cells throughout which blood was extravasated." "Some of the groups of cells had an open center filled with uncoloured, finely vacuolated material, and the peripheral elements and the groups were furnished with oval nuclei set vertically to the tissue around. It was suggestive that the cells had arisen from the columnar epithelium of the ducts and had retained some of their property of forming mucin." That this material was mucin was not proved by special stains. "Dr. S. G. Shattock kindly examined the section and pointed out the evidence showing the tumor to be fairly conclusively a duct carcinoma." But the rosette structure of neuroblastoma often has been mistaken for epithelial tubules, and the gross appearance of the liver, mottled with small

purplish areas, is much more like a neuroblastomatous invasion than like primary bile duct carcinoma, which usually produces a large pale growth, and if there are intrahepatic metastases they are usually pale nodules spreading out from a primary growth and not diffuse purplish areas. That the author was not considering the possibility of neuroblastoma is indicated by his including in his review of primary cancers of the liver the cases of Parker, Dalton, Heaton and Pepper, which were all cases of secondary neuroblastoma. In reply to a letter of inquiry Dr. Dansie has written me that in performing the autopsy he took great care to exclude the presence of any primary growth outside the liver. This may be a case of diffuse intrahepatic neuroblastomatosis without any primary tumor present outside the liver.

One is therefore obliged to question all the lesions usually cited as examples of congenital carcinoma of the liver and conclude that, despite the rather considerable number of examples of true carcinoma of the liver in children, usually not much before puberty, there are few, if any, that may be considered as having been proved to be present as carcinoma at birth. A possible exception is offered by the tumor mentioned by A. O. Singleton, of Galveston, Texas. In discussing a paper by F. W. McRae, in 1935, he said that he had removed from the liver of a 17 day old infant a tumor which weighed 175 Gm. and which was said to have been diagnosed as adenocarcinoma of the liver by James Ewing. The tumor had been noted immediately after birth, and the child was well at 3 years.

Dr. Singleton has furnished me with a block of this tumor. It presents two growing elements about a central necrotic area. The inner regions of the peripheral growing zone are occupied by an angiomatous structure, much resembling an invasive hemangioendotheliomatous tumor of the liver, such as that reported by Veeder and Austin, which I have examined. At the periphery are areas of atypically arranged cords of liver cells, generally intermingled with the advancing edge of the angiomatous process, which may account for the atypical arrangement. No normal liver tissue is present in the specimen examined. Dr. Joseph McFarland, who also examined this tumor, suggests that it may be "a congenital malformation of the liver with various secondary distributions such as angiectasis, thrombosis, necrosis, and fibrosis." I am inclined to agree with this view, with the addition of "adenoma-like arrangement of adjacent liver tissue," which apparently is in response to stimulation by the angiomatous growth. Dr. Ewing also failed to find evidence of malignancy, for he reported, "The structure does not vary very much from normal liver tissue and I would call it an adenoma. Yet all these liver adenomas are apt to get loose in the blood vessels so that the prognosis is doubtful." As the child was well 3 years after operation, and there is no positive microscopic evidence of malignancy, this case cannot be considered as a proved case of congenital carcinoma.

A more probable exception is furnished by the case published by Ganelli and Predaroli. The patient was a girl, with the liver palpable on the seventh day, who died at 5½ months with the liver weighing 750 Gm. because of a large single tumor. The other organs were normal. The tumor was reported as adenocarcinoma of the liver, but the cells were so small and undifferentiated as to make this diagnosis questionable—as does the absence of extension or metastasis—although the gross appearance supports it.

Only a few authentic instances of carcinoma of the liver have been reported at such an early age as to suggest prenatal malignancy. Perhaps the best authenticated of these are:

1. McRae (1935). A boy at 3½ months had abdominal enlargement. At 6 months a tumor weighing 322 Gm. was resected from the right lobe of the liver, and death occurred five days later. The tumor was apparently malignant teratoid hepatoma, as it was described as malignant liver cell adenoma with areas of osteoid tissue and a small area of keratinized epithelium. No metastases were found at necropsy.

2. Condat, Gadrat and Laserre (1937). A boy died at 3½ months. At 3 months the abdomen was greatly distended, with the collateral vessels dilated, suggesting that the growth had then become far advanced and possibly had arisen after birth. The liver weighed 610 Gm., including the tumor, which was a primary malignant liver cell tumor. There were no metastases.

3. Petrone (1907). A girl was noted at 3½ months to have enlargement of the abdomen. She died at 4 months. Necropsy disclosed a large tumor of the right lobe of the liver with metastasis in the lung, but no tumors elsewhere. The diagnosis was adenocarcinoma.

4. Ribbert. In the abstracts of a society meeting he is quoted as referring to a 4 month old infant with a large hepatic tumor, the cells of which contained bile, diagnosed true malignant hepatic adenoma. I can find no more complete report of this case.

5. Pirie (1932). A boy suffered with feeding difficulties and vomiting and had an enlarged abdomen from the time of birth. When this child was examined at 8 months, the abdomen was greatly distended and the collateral veins were prominent. Death occurred the next day. The liver with a large solitary tumor weighed 550 Gm. Microscopically, the tumor consisted "essentially of large polyhedral to spherical cells, the arrangement of which resembled liver tissue. Numerous mitotic figures were observed. The diagnosis was "primary carcinoma of the liver." Nothing is said about other organs, so presumably there were no metastases.

6. Pirie (1932). This tumor occurred in a boy, who was also observed at 8 months. The mother stated that the abdomen had been enlarging progressively since birth. There had been frequent vomiting. As in the previous case, the collateral veins were distended over the protruding abdomen and chest. "The abdomen was opened and a large mass found, immediately connected with the liver. The child died within twenty-four hours." At necropsy the pathologic features were practically the same as in case 5. "Dr. Erb reported the tissue to be carcinoma of the liver."

7. Steiner (1938). A girl who died at 4 months had a liver weighing 450 Gm. Microscopically, malignant hepatoma was found, with emboli in the pulmonary vessels. This infant had been well until four days before death.

8. Wollstein and Mixsell (1919). A girl in whom swelling of the abdomen was noted at the third month died at 5½ months with the liver weighing 860 Gm. The tumor was mostly in the right lobe, with metastases in the left lobe and in the lung. It was hepatoma, not very anaplastic, but undoubtedly malignant, and probably congenital, since its structure suggested slow growth.

9 and 10. Webster (1938). The patients were male infants; in one the tumor was diagnosed at the age of 6 months, the mother having noted abdominal swelling for three months; in the other, at 4 months, the abdominal enlargement having been noted for two weeks. The tumors were both malignant hepatoma.

CONGENITAL HEPATIC HEMANGIOENDOTHELIOMA

A few cases of what seems to be true malignant hemangioendothelioma of the liver have been reported in which the malignancy appears to have been congenital, and this rare tumor seems to be one that usually arises early in life or not at all. Some of the best authenticated cases are the following:

1. Veeder and Austin (1912). A girl with abdomen distended since birth died at 10 weeks. She was one of twins, but whether identical twins or not is not stated; the other twin was not reported as having any similar condition. The liver weighed 943 Gm. and contained a cavernous hemangioma of a type which Mallory considered to be true blastoma in that the tumor grows by proliferation of endothelial cells. No other organs were involved. These authors expressed the belief that the cases reported by Chervinsky and by Bruchanow were of the same character.

2. Chervinsky (1885). The case concerned an infant with abdomen enlarging from shortly after birth until death at 6 months, when the liver weighed 943 Gm. From the published description and illustrations I cannot be sure whether the multiple hemangioendothelioma was malignant or not.

3. Bruchanow (1899). The infant lived but 15 weeks, when the liver weighed 710 Gm. There were also a few angiomas of the skin.

4. Orzechowski (1927). A girl dying at 2½ months, who had been icteric since birth, is reported to have had malignant hemangioendothelioma of the liver with metastases to the lung and skin.

5. Ruggeri (1935). A boy born with a distended abdomen died on the twenty-seventh day. The liver weighed 585 Gm. because of "immature hemangioendothelioma."

6. De Haan (1903). An infant (sex not stated) was noted at 10 weeks to have a swelling of the abdomen due to enlargement of the liver. At death, on the ninety-fifth day, the liver weighed 867 Gm. and contained many blood-filled cysts which were believed to have been produced by malignant hemangioendothelioma, a conclusion justified by the histologic examination.

7. Foote (1919). A male infant, observed to have an enlarged abdomen at 2 months, died following laparotomy, at 3 months. The liver weighed 750 Gm.

and contained a tumor, diagnosed as hemangioendothelioma, in which were many mitotic figures. There were no tumors in any other organ.

8. Bondy (1911). An infant had abdominal swelling, which the mother noted first at the third week. When this child was examined by a physician at 4 weeks, the upper three fourths of the abdomen was filled by a greatly enlarged liver. A laparotomy revealed a tumor of the liver, diagnosed as angiosarcoma, which was not removed, and no other tumors were found at operation. The child died at 3½ months. No necropsy was made. (This case has been indexed repeatedly as a case reported by "Bong").

9. Hewlett (1899). A boy whose abdomen was prominent at 3½ months died ten days later. The liver weighed 19½ ounces (643 Gm.) and was studded with nodules, many of which were hemorrhagic. The lungs contained many metastases, up to 1½ inches (3.5 cm.) in diameter. Other organs were normal. The microscopic description suggests malignant hemangioendothelioma. The case was reported as one of primary sarcoma of the liver.

10. Jorge and Brachetto-Brián (1933). A 5 months old infant had an enormous liver. A biopsy specimen was taken, which exhibited what was diagnosed as hemangioendotheliosarcoma, a diagnosis corroborated by the illustrations. The abdomen had been noted to be enlarged shortly after birth and had continued to enlarge. Death followed shortly after the biopsy. There was no necropsy.

Other malignant vascular endothelial tumors of the liver in young infants, possibly congenital, have been reported. Kunstadter observed such a tumor in an infant at 5 months (liver weight, 765 Gm.); Geschickter and Keasbey, one in an infant at 9 months. Gödel reported in abstract the case of an infant of 3 months with typical multiple hepatic hemangioendothelioma, the liver measuring 15 by 8 by 4.4 cm., but gave no other information. Arthur Stern reported a case of cavernous hemangioma largely replacing the liver of a 6 week old girl, but gave no information that enables one to decide whether this growth was malignant. Taylor and Moore reported observing multiple hemangioma in a 3 month old girl, whose death occurred at 5 months; they could not decide whether the growths were malignant or not. The "malignant angiomatosis" in a jaundiced Javanese infant described by Soewadji Prawirohardjo and Soetarto may well have been primary in the liver, although permission for necropsy was not obtained.

HEPATIC TUMORS THE CONGENITAL OR MALIGNANT NATURE OF WHICH IS IN DOUBT

The literature contains reports of a few other primary malignant tumors of the liver in early infancy, from which, for one reason or another, it is quite impossible to decide exactly what the tumors were, although some of them may really have been malignant hepatic neoplasms. Among these may be mentioned the following:

1. Argueta (1933). The author reported the tumor as primary carcinoma of the liver in a 2 month old infant whose abdomen had been enlarged since birth. Permission for necropsy was refused, but the abdomen was opened "clandestinely" and a piece of liver removed. The histologic character was described as "more epithelial than lymphoid." While this was undoubtedly a congenital neoplasm, inadequate study and reporting leave its nature in doubt.

2 and 3. Alsina (1926). The first and the second child in an apparently healthy family each presented a large tumor in the liver at birth, fatal after twenty-one and thirty-six days. Alsina said that he had encountered 2 other cases of this kind, but as necropsy was not allowed the nature of the enlargements cannot be known.

4. West (1853). This author is frequently quoted as having reported a congenital sarcoma of the liver, but in his book on pediatrics he reported a girl of 8 months with a tumor of the liver, death occurring at 1 year, in whom necropsy disclosed a large soft brainlike tissue growth in the right lobe of the liver with pulmonary metastases. He called it a mixture of "carcinoma medullare and carcinoma fasiculatum." The evidence does not establish either the nature or the congenital presence of this tumor.

5. Prescott (1895). This writer is cited as having reported a case of congenital malignant adenoma of the liver. This tumor seems to have been that of a patient of R. W. Lovett's, a 5 month old infant. The tumor, 8 cm. in diameter, involved the right lobe of the liver and perforated into the stomach. It was examined in the Boston City Hospital by Mallory. Microscopically, it was described as chiefly epithelial with some sarcomatous elements, therefore perhaps teratomatous. It was thought to have originated early in fetal life, but symptoms were not observed until the fourth month.

6. Mikula and Klein (1928). A tumor was found in a 1 month old infant which the authors considered to be a combination of bile duct and liver cell carcinoma, but as mention is made of the presence of rosettes the possibility exists that this may have been neuroblastoma.

7. Gross (1857). This author is often quoted as having reported a scirrhous carcinoma of the liver in a 3 month old child, but it is probable that this was cirrhosis with regenerative hyperplasia, which often in the past has been mistaken for carcinoma.

8. Frerichs (1861). This author has often been cited as reporting a case of carcinoma of the liver in an infant, but the reference given refers to a woman with cancer of the breast, who died with acute yellow atrophy of the liver at the seventh month of pregnancy, the fetus showing "nichts ungewöhliches."

Not a few times teratoma has been found in the liver at birth or soon after, and in some instances has been listed as a congenital malignant growth because the reporter diagnosed sarcomatous elements in it. But since in teratoma, especially so near fetal life, there commonly are undifferentiated tissues, especially neuroblastic elements much resembling sarcoma, the diagnosis of malignancy on histologic appearance alone, in the absence of metastases, is open to doubt. Among such cases is the following:

Nissel, in 1926, reported a mixed tumor of the liver which ruptured shortly after birth, causing fatal hemorrhage. It contained cartilage, bone, epithelium, and "connective tissue components of apparently malignant character." He also said that it showed "pictures which did not permit one to exclude a sarcomatous nature for these parts," showing a caution not exhibited by some compilers who have listed this among congenital malignant tumors of the liver. There were no metastases.

CONGENITAL SARCOMA

Although the old idea that sarcoma is a disease of youth and carcinoma a disease of old age is now known to be incorrect, the fact remains that true sarcoma is vastly more likely to occur in childhood than carcinoma, and in seeking cases of congenital sarcoma no less than 150 possible cases have had to be considered, not including the cases of mixed tumor of the kidney and the cases of hemangioendothelioma of the liver. The tumors that seem to be certainly congenital sarcoma are given in table 7 and number 29. It is to be noted that even at this early age not a few were successfully removed, without recurrence. They were found in many sites and of varying histologic structure, differing in no particular respect from the types of sarcoma found in later years except that the proportion of bone sarcoma is perhaps lower.[5]

In table 8 are listed 20 tumors which probably were truly congenital sarcoma, although the evidence lacks something needed to establish this completely, as explained in the comment on each case. Many of the cases are inadequately reported, and a few were reported in journals which could not be obtained to amplify the inadequate material furnished by the available abstracts.

Table 9 contains data on 46 tumors that may possibly have been congenital sarcoma. Many of them have been published as such, and subsequently cited as such in various compilations, but for one reason or another they cannot be considered as completely proved, or even established as most probably belonging in this category. In this group have been included several tumors which on the basis of clinical or necropsy reports very probably *were* sarcomatous, but the authors' conclusions were not confirmed by any recorded microscopic study. Some were truly sarcomatous but were not noted at birth or early enough to prove that they were really congenital. Some were undoubtedly congenital malignant tumors, but that they were sarcomatous could not be determined from the evidence submitted; neuroblastoma has often been called lymphosarcoma and round cell sarcoma. Some are included because, although not noted at birth, they were of a size or a location when first observed that suggested the possibility or probability that they really had begun before birth. In this group, especially, the scarcity of bone sarcoma is noteworthy.

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5. It is of interest to mention that W. R. Williams (Natural History of Cancer, New York, William Wood & Company, 1908, p. 90) said: "Penberthy has met with a sarcoma of the chest wall in a newly born foal, and Crisp has seen a large encephaloid tumor on the chest of a lamb." In Penberthy's case (1902) the tumor was resected at 1 month but recurred, and when the animal was killed there were many metastases in the lungs and pleura. T. Purmann (Beitr. z. path. Anat. u. z. allg. Path. **84**:659, 1930) reported as malignant endothelioma of the peritoneum a tumor found in a calf 6 to 8 weeks old. This tumor was so large (450 Gm.) and extensive that it almost certainly was congenital.

TABLE 7.—*Congenital Sarcoma*

No.	Age When Observed	Age at Death	Sex	Author	Primary Site	Metastases	Type	Comment
1	Birth	24 hours	M	Adam and Moriot: Rev. internat. de chir. **31**: 46, 1920	Orbit	None	Perivascular round cell	Arose in floor of orbit; involved bones of face and skull. Size of half orange
2	Birth	4 months	F	Amolsch: Arch. Path. **24**: 777, 1937.....	Vulva	Mediastinum, lungs, scapular region	Myxosarcoma	Grew progressively; removed; no local recurrence. Atresia of tricuspid valve
3	At full term	2 days	F	Corten: Frankfurt. Ztschr. f. Path. **24** (supp.): 693, 1921	Brain	None	Angiosarcoma	Involved left cerebral hemisphere; half size of man's fist
4	Birth	?	?	Delbanco: München. med. Wchnschr. **45**: 155, 1898	Tongue	None	Spindle cell	Removed at 14 days. Description supports diagnosis. Outcome not stated
5	?	7 days	M	Eichler: Frankfurt. Ztschr. f. Path. **36**: 326, 1928	Pancreas	None	Lymphosarcoma	Hen's egg size (8.7 × 5.5 × 5.5 cm.), infiltrating all but tail of pancreas. All other organs normal
6	Birth	6.5 months	F	Fisk: Arch. Pediat. **13**: 261, 1896.....	Subcutaneous interscapular space	Axillary glands	Large round cell	Subcutaneous tumor removed at 7 weeks. Rapid recurrence, size of child's head at death. No necropsy
7	Birth	Recovered	M	Geschickter: Personal communication to the author	Upper arm	None	Oat cell	Size of large orange at birth. Excision. Patient well two years later
8	Birth	Recovered	F	Geschickter and Copeland: Tumors of Bone, New York, 1931, p. 557	Humerus	None	Spindle cell	Amputation at 6 mo. Patient well 10 yr. later
9	13 days	3 months	?	Geschickter and Copeland: Tumors of Bone, New York, 1931, p. 156	Femur	?	Osteogenic	Diagnosis: Congenital sclerosing osteogenic sarcoma
10	Birth	3 days	M	Giafaml: Patologica **6**: 812, 1914.....	Neck	Subcutaneous	Angiofibrosarcoma	Size, 4 cm. in diameter. Location, below left ear, independent of parotid. Numerous subcutaneous but no visceral metastases. Possibly neurogenic
11	Birth	Recovered	M	Göbel: Arch. f. klin. Chir. **87**: 191, 1908....	Femur, periosteum	None	Spindle cell	Removed by operation after 3d week. Site irradiated. Recovery
12	Birth	Recovered	F	Goller: Ueber einen Fall von congenitalem reinem Sarkom der Parotis, Thesis, Würzburg, A. Boegler, 1898	Parotid	None	Angiosarcoma	Grew steadily to walnut size at 4 mo., infiltrating. Removed. No immediate recurrence. Reported by a pupil of Rindfleisch and Borst
13	Birth	Recovered	M	Hudson: Am. J. Cancer **26**: 568, 1936.....	Foot, bone	None	Fibrosarcoma	Replaced 4th left metatarsal. Size of lemon. Amputated on 11th day. Patient well at 8th month
14	Birth	3.5 months	?	Kanno: Ein neuer Fall von kongenitalem zungensarkom, Thesis, Berlin, 1933	Tongue	None	Spindle cell	Grew rapidly; removed at 2 mo.; recurred in 2 weeks; resected 1 mo. later. Patient died after one week

15	Birth	Recovered	M	King: Lancet **2**: 706, 1905	Fibula	None	Spindle cell	Hazelnut size at birth; grew rapidly and ulcerated. Amputation at 3½ mo. Patient well 4 yr. later
16	Birth	Recovered	F	Kolodny: Arch. Path. **1**: 524, 1926	Tibia	None	Fibrosarcoma	Arose in head of tibia, periosteal. Amputation at 8th week. Patient well at 8 yr.
17	Birth	?	?	Kubanyi: Zentralbl. f. Chir. **62**: 2126, 1935	Axilla	Axillary glands	Fibrosarcoma	Removed 9th day. Weight, 112 Gm. Infiltrated skin and axillary glands. Outcome not stated
18	Birth	Recovered	?	Listo: Duodecim **54**: 264, 1938	Upper lip	None	Spindle cell	Cherry size at birth. Removed at 3¼ weeks when it filled entire upper lip. Radium used after operation. No recurrence 8 mo. later
19	Birth	16 months	?	Lombard and LeGenissel: Rev. d'orthop. **21**: 297, 1934	Forearm	?	Spindle cell	Size of large orange at birth. Reduced by radiation but later enlarged. Amputation and death at 16 mo. No necropsy
20	Birth	?	F	Meerovitch: Bull. Assoc. franç. p. l'étude du cancer **25**: 710, 1936	Thigh	?	Fibrosarcoma	Size of infant's head at birth, caused dystocia. Destroyed ⅓ of femur in 4 mo. Biopsy Duration not stated
21	Birth	?	M	Moldovan: Prag. med. Wchnschr. **30**: 403, 1905	Calf	?	Spindle cell	6 × 6.5 × 4 cm. Removed by operation on 5th day
22	Birth	3 months	?	Naegele: Ueber Zungensarcom mit besondere Berücksichtigung des Kinderalters, Thesis, Kiel, P. Peters, 1900	Tongue	None	Round and spindle cell	Removed at 3 mo., 3.5 × 2 cm. Invaded muscle and mucosa. Patient died of pneumonia
23	Birth	Birth	M	Pohjala: Duodecim **54**: 185, 1938	Orbit	Subcutaneous	Round cell	Hen's egg size, pushing eye forward but not invading it. Invaded cranial and nasal cavities. Several subcutaneous metastases
24	Birth	Recovered	?	Rehn: Chirurgen-Cong. **1**: 121, 1890	Foot	None	?	Amputated at 14 days; recovery. Weigert diagnosed sarcoma
25	Birth	Recovered	?	Sherwood: Ann. Surg. **77**: 771, 1923	Humerus	None	Periosteal	Pathologic fracture at birth; shoulder disarticulation at 3 weeks. Patient well 31 mo. later. Case 68, Codman sarcoma registry
26	Birth	4 days	?	Stern: Berl. klin. Wchnschr. **31**: 802, 1894	Small intestine	None	Round cell or angiosarcoma	Abdomen distended at birth; 4-5 cm. of bowel involved
27	Birth	8 days	M	Wachs: Zentralbl. f. Chir. **64**: 1352, 1937	Prostate	None	Rhabdomyosarcoma	Distention of abdomen and urinary obstruction from birth. Cystostomy. Tumor 5 × 4 cm.
28	Birth	7 months	?	Weinlechner, in Gerhardt, C.: Handbuch der Kinderkrankheiten, Tübingen, H. Laupp, 1887, vol. 6, p. 210	Shoulder	?	Fibrosarcoma	Removed at 7 mo. Size 11 × 15 cm. Death from infection. Diagnosed by Chiari
29	Birth	6 weeks	?	Winogradow: Med. obozr.; abstracted, Centralbl. f. Chir. **25**: 536, 1898	Back skin	?	Small round cell angiosarcoma	At birth, walnut size; at death, size of child's head

TABLE 8.—*Probably Congenital Sarcoma*

No.	Age When Detected	Age at Death	Sex	Author	Site	Metastases	Type	Comment
1	Birth	?	?	Arkövy: Orvosi hetil., Feb. 4, 1883; abstracted, M. Rec. **23**: 351, 1883	Lower jaw	?	Large cell	Size of walnut. Data from abstract (New York M. Rec. **23**: 351, 1883); original article not available
2	Birth	10 days	?	Baccarini: Ann. ital. di chir. **2**: 495, 1923...	Tongue	None	Round cell	Size 2.5 × 3 × 2 cm.; filled mouth at birth. Infant died of pneumonia. Cystic spaces suggest lymphangioma, but diagnosed sarcoma
3	Birth	3 months	?	Brailey: Lancet **1**: 248, 1880.....	Orbit?	None	Alveolar sarcoma	Invaded roof of orbit, right anterior cerebral lobe, and pushed forward eye, which was not involved. Reported as tumor of brain and optic nerve, but probably was orbital sarcoma
4	Birth	?	?	Cayse: J. Tennessee M. A. **13**: 407, 1921....	Orbit	?	Small round cell	Attached to orbital ridge, infiltrated muscle. Outcome not stated. Report inadequate
5	Birth	20 days	F	Charon and Ledeganck: Bull. Acad. roy. de méd. de Belgique **12**: 512, 1878	Orbit	Many (see comment)	Small round cell	Size of hen's egg at birth. Became ulcerated. Arose from internal angle of orbit, not involving eye, optic chiasma of brain. Miliary tumors in pleura, pericardium, mediastinum and subcutaneous tissue. Possibility of neuroblastoma not excluded by report
6	Birth	Recovered	M	Curtis: Arch. Pediat. **20**: 448, 1903.....	Scapula	None	Spindle and round cell	Size of hen's egg at birth. Removed at 5½ mo. Inadequate report
7	1 day	Recovered	M	Deming: J. A. M. A. **80**: 902, 1923.....	Kidney	None	Spindle cell	Blood in urine 1st day. Abdomen large since birth. Nephrectomy at 29 days. No recurrence. No evidence of nephroma, but this is difficult to exclude
8	Birth	6 weeks	F	Jeanneret: Des tumeurs malignes du pharynx chez l'enfant, Thesis, Basel, 1914..	?	Many	Round cell or lymphosarcoma	"Des tumeurs malignes du pharynx chez l'enfant," but autopsy showed tumors in liver, intestine, lung, lymph nodes, adrenal, muscles, subcutaneous tissue, as well as pharynx, so primary site is uncertain. Probably lymphosarcoma
9	Birth	Recovered	?	Krause: Deutsche med. Wchnschr. **36**: 343, 1910	Abdominal wall	None	Spindle cell	Size of pigeon's egg. Surface became necrotic. Extirpated. No recurrence. Report inadequate
10	Birth	Recovered	M	Lücke: Arch. f. klin. Chir. **90**: 862, 1909...	Forearm	None	Spindle cell	Hazelnut size at birth. Grew rapidly. Removed at 3 mo. No recurrence in 3 mo., although removal seemed perhaps inadequate
11	14 days	11 weeks	?	Maas, cited by Croner: Ztschr. f. Krebsforsch. **12**: 442, 1913	Thigh	Inguinal glands	Telangiectodes	Croner, of Maas's clinic, reports this briefly. Infant operated on at 10 weeks, died 6 days later. Size of tumor at 14 days indicates congenital origin

12	12 days	?	?	Mayou: Ophth. Rev. **29**: 31, 1910.....	Orbit	?	Spindle cell	At 12 days filled and protruded from orbit. Removed, recurred, reoperated on after 3 mo. Child then lost sight of
13	5 days	10 weeks	M	Neuhaus: Arch. f. Kinderh. **21**: 367, 1897...	Leg	Subcutaneous glands, muscles, heart, kidney, thymus	Round cell	At 5 weeks egg-sized mass removed. Then subcutaneous nodules appeared and became abundant
14	Birth	4 weeks	M	Perera: Lancet **2**: 14, 1919.....	Subcutaneous?	Widespread	Round cell	Innumerable subcutaneous tumors; also tumors in lymph glands, periosteum of many bones, liver, spleen, kidney, especially retroperitoneal glands. Probably lymphosarcoma
15	Birth	2 years	F	St. Germain: Rev. mens. d. mal. de l'enf. **1**: 26, 1883	Forearm	?	Sarcoma	Removed repeatedly. Seemed cured. Child died at 2 yr. of pneumonia. No necropsy
16	Birth	3 hours	M	Schlossbann: Frankfurt. Ztschr. f. Path. **25**: 486, 1921	?	Widespread especially subcutaneous, liver, stomach, ribs	Round cell	Body covered with tumors; tumors in almost all internal organs, also no definite primary tumor. Blood not leukemic. Necropsy by Beitzke.
17	Birth	?	M	Stübinger: Kausuistischer Beitrag zur Kenntnis der angeborenen bösartigen Geschwülste, Inaug. Dissert., Leipzig, B. Georgi, 1903	Foot	Inguinal glands?	Angiosarcoma	Bluish tumor size of hazelnut at birth. Removed 17 weeks later, walnut size. Some enlarged inguinal glands. Outcome not stated
18	At full term	Deadborn	?	Tavella: Ann. di ostet. e ginec. **58**: 953, 1936	Thorax	?	Angiosarcoma	Attached to chest wall but not lung. Pictures indicate malignancy, but do not exclude neuroblastoma
19	Birth	4.5 months	F	Tullian: Contribution à l'étude des sarcomes congénitaux, Thesis, Nancy, no. 35, 1899	Subcutaneous	Cervical glands	"Embryonic sarcoma"	At birth, size of mulberry. At 2 mo., 5 × 4 cm. Excised. At death all cervical nodes enlarged
20	Birth	7 months	M	Weinlechner, in Gerhardt, C.: Handbuch der Kinderkrankheiten, Tübingen, H. Laupp, 1887, vol. 6, p. 210	Shoulder, subcutaneous	?	Fibrosarcoma	Removed at 7 mo. 11× 15 cm. Infant died of infection. Diagnosed by Chiari

TABLE 9.—*Possibly Congenital Sarcoma*

No.	Age When Seen	Age at Death	Sex	Author	Site	Metastases	Type	Comment
1	Birth	?	F	Aviragnet and Coyon: Ann. de dermat. et syph. **6**: 619, 1905	Skin	Cutaneous	Angio-sarcoma	At birth pea-sized nodule on neck. Removed at 2½ mo. and then became disseminated all over surface of body. Sarcoma with large nuclei and giant cells. Infant living at 6 mo. Report inadequate
2	2 months	?	?	de Beurmann and Gougerot: Ann. de dermat. et syph. **7**: 392, 1906	Skin of temple	Cutaneous	Round cell (type Perrin)	First observed in subcutaneous tissue. At 6 mo. there were 100 tumors. Biopsy. No other information
3	2 months	2 months	F	Branch: Am. J. Path. **9**: 777, 1933.....	Spleen, kidneys, intestine	?	Lympho-blastoma ?	Symptoms first at 2 mo. Death followed exploratory laparotomy. Spleen 85 Gm., kidneys 112 Gm. each. Intestine and appendix involved. No study of other organs. Blood contained great numbers of lymphocytes. Probably leukemia
4	Premature	Birth	F	Breinl: Prag. med. Wchnschr. **28**: 543, 1903	Dura spinalis	No	Round and spindle cell	Grew into abdomen as tumor size of man's fist. 6 mo. fetus. All organs normal. May have been neuroblastoma
5	Birth	6 months	?	Bryant: Guy's Hosp. Rep. **20**: 341, 1875...	Upper jaw	Skin	?	Present at birth. Orange size at 4 mo. Infant died at 6 mo. No microscopic study or necropsy. Numerous cutaneous metastases
6	Birth	14 months	M	Bryant: Guy's Hosp. Rep. **20**: 341, 1875...	Lower jaw	?	?	Size of walnut at birth. Orange size at 5 mo. Apparently these two tumors arose from bone itself. Called sarcoma without microscopic examination or necropsy
7	3 months	6 months	F	Carpenter: Arch. Pediat. **12**: 270, 1895.....	Dura	Lungs	?	At necropsy tumor size of closed fist arising in dura, involving left cerebral hemisphere. Metastases in both lungs. No microscopic study
8	5 days	82 days	?	Castellana: Policlinico (sez. prat.) **32**: 1709, 1925	Leg	Inguinal glands, subcutaneous	?	Swelling of left leg noted at 5 days. Diagnosis was sarcoma with metastases to inguinal and axillary glands and left scapular region. No biopsy, necropsy or blood examination. Clinical diagnosis only, but probably correct
9	5 weeks	Recovered	F	Chambers: Univ. M. Mag. **2**: 376, 1890.....	Breast	None	Round cell	Grew steadily until size of small hen's egg. Removed at 4 mo. No recurrence in 5 mo.
10	23 days	1 month	?	Choisser: U. S. Nav. M. Bull. **20**: 451, 1924	Soft palate	Regional glands	Fibro-sarcoma	No necropsy. Not known whether growth began before birth
11	1 day	1 day	?	Comba: Clin. mod., Firenze, 1901, vol. 7; abstracted, Jahrb. f. Kinderh. **54**: 778, 1901	Rectum	?	Small cell	Involved mucosa of rectum. Soft ulcerated polypoid growths. Original article not accessible. Abstract inadequate
12	Birth	?	?	Dawson: Am. J. Obst. **12**: 160, 1879.....	Femur	?	Myxosarcoma ?	Orange size at birth, grew rapidly, became ulcerated. Diagnosis confirmed by A. Jacobi. No microscopic study. At 7 weeks child declining rapidly

				coma ?				incerated. Diagnosis confirmed by A. Jacobi. No microscopic study. At 7 weeks child declining rapidly
13	?	8 weeks	?	de Lange and van Goor: Nederl. tijdschr. v. geneesk. **2**: 828, 1921	Mediastinum	Liver	Lymphosarcoma	Tumor 2.4 × 5.6 × 6.7 cm. in posterior mediastinum. Adrenals normal
14	Birth	4 months	?	Fazzini: Gazz. internaz. méd.-chir. **33**: 92, 1928	Forehead	Regional glands	Angiosarcoma	Size of "large egg" at birth; removed at once. Regional nodes enlarged at death from cachexia. No necropsy
15	Birth	9 weeks	?	Frank: Prag. med. Wchnschr. **19**: 17, 1894	Sacral region	Local	Myxosarcoma	A sacral teratoma containing myxosarcomatous areas, proved malignant by metastasis in ischiorectal fossa. Diagnosis confirmed by Chiari
16	Birth	?	M	Fuss and Mommsen: Kinderärztl. Praxis **7**: 403, 1906	Tonsil	?	Undifferentiated	Child born asphyxiated, bleeding from walnut size tumor of tonsil. Tumor removed but recurred at 5 weeks; removed by coagulation. Patient not followed
17	"Early weeks"	6 months	F	Garot: Rev. franç. de pédiat. **5**: 491, 1929	Retroperitoneal lymph nodes ?	Liver, kidney, appendix	Lymphosarcoma	Abdomen enlarged in early weeks. "Enormous" tumor below right kidney. Arose in right lumboiliac region. Possibly neuroblastoma, but adrenals not involved
18	?	1 month	F	Harvey and Tennant: Am. J. Path. **10**: 123, 1934	Bladder	None	Neurogenic sarcoma	Mother too unintelligent to give history. Tumor invaded vesicovaginal tissues and cervix
19	12 weeks	Recovered	F	Hecker: Zentralbl. f. Chir. **55**: 842, 1928....	Gluteal muscle	None	Spindle cell sarcoma	Cherry size when noted by mother at 12 weeks; so congenital malignancy doubtful. Removed; recurred in 3 weeks; again removed; no recurrence 4 mo. later
20	Birth	Recovered	?	Holmes: Tr. Path. Soc. London **12**: 206, 1861	Neck	None	Round cell	Tumor 2 × 2 × ¾ inch (5 × 5 × 2 cm.) at 14th day. Removed. No recurrence ½ yr. later
21	Death	9 days	F	l'Huillier: Virchows Arch. f. path. Anat. **178**: 507, 1904	Pancreas	None	Lymphosarcoma ?	Tumor 3.2 × 2.1 cm., replacing head of pancreas. Lymph nodes not involved. Neoplastic nature doubtful. Contained giant cells. Very dubious diagnosis
22	Birth	Recovered	?	Jacobi: M. Rec. **19**: 217, 1881.....	Eyelid and temple	?	Angiosarcoma ?	Malignant nature uncertain. Information inadequate. Very doubtful
23	1 month	?	M	Jacobi: Arch. Pediat. **14**: 801, 1907.....	Scrotum	Subcutaneous	Giant cell	Noted 1 mo. after birth. Many other subcutaneous tumors appeared. Prudden diagnosed giant cell sarcoma. Subsequent course not stated
24	Birth	Recovered	M	Jacobi: Am. J. Obst. **2**: 81, 1869-1870.....	Tongue	None	"Fusocellulare"	Hazelnut size at birth, walnut size when removed at 11 weeks. Later course not given
25	4 weeks	5 weeks	?	Jonker: Maandschr. v. kindergeneesk. **2**: 302, 1934	Posterior mediastinum	Lung	Small round cell	At 4 weeks respiratory difficulty and dulness beside sternum. Metastases to lung. All other organs, including thymus and adrenals, normal. Possibility of neuroblastoma not considered
26	4 weeks	Recovered	?	Joseph: Deutsche med. Wchnschr. **29**: 621, 1903	Abdominal wall	None	Round and giant cells	Grew slowly. Hazlenut size when removed at 5 mo. Smooth muscle cells mixed with sarcoma cells. Considered embryonal tumor with malignant degeneration

TABLE 9.—*Possibly Congenital Sarcoma—Continued*

No.	Age When Seen	Age at Death	Sex	Author	Site	Metastases	Type	Comment
27	Birth	?	?	Karewski: Deutsche med. Wchnschr. **21** (supp.) : 35, 1895	Subcutaneous	Subcutaneous, muscles	Angiosarcoma	At birth numerous tumors over entire body, not regularly related to nerves or vessels. At 17 weeks some were fist size. One removed recurred. Some were sarcomatous, some angiomatous. Abstract only available. Complete report promised but could not be found
28	Birth	Recovered	?	Kopfstein: Časop. lék. česk. **43** : 36, 1904; abstracted, Centralbl. f. Chir. **32** : 24, 1905	Skin	None	Angiomyxofibrosarcoma	Walnut size. Removed at 5 days. No recurrence in a year. Original article not available. Abstract inadequate
29	Birth	?	F	Letailleur: Contribution à l'étude du sarcome des enfants, Thesis, Lille, ser. 4, no. 115, 1895	Lower jaw	Regional glands	?	"Size of a nut" at birth, with an enlarged subhyoid gland. Continued growth. Tumor and gland removed at 3 mo. No recurrence 4 mo. later. Diagnosed sarcoma without microscopic examination
30	Birth	Recovered	M	Mandillon: Bull. et mém. Soc. de chir. de Paris **4** : 160, 1878	Shoulder	None	Fibroplastic	Size of "small orange," pedunculated; removed by thermocautery; no recurrence 3 mo. later. Microscopic description inadequate for diagnosis
31	2 weeks	Recovered	?	Marshall: Tr. Path. Soc. London **29** : 215, 1878	Leg muscles	None	Spindle cell	Swelling of calf muscles noted by mother at 2 weeks. Amputation at 5 mo. Well 6 mo. later
32	15 days	4 months	F	Morquio: Arch. de méd. d. enf. **37** : 29, 1934	Subcutaneous	Subcutaneous	Lymphosarcoma ?	Grew rapidly all over body except head, and became 2-3 cm. before death at 4 mo. from scarlet fever. No necropsy. Biopsy "a question of reticulo-lympho-sarcoma type or a reticulo-polyblastoma." But blood cells 77 per cent lymphocytes !
33	7 months' fetus	Premature	F	Nyhoff: Zentralbl. f. Gynäk. **35** : 808, 1911..	Intra-abdominal	?	Sarcoma	"Half fist size" tumor adherent to intestines, pancreas, left kidney. "Perhaps from left kidney or adrenal, perhaps arising in the pancreas." No more information. Report very inadequate. Probably neuroblastoma
34	Birth	12 weeks ?	?	Paul: Lancet **1** : 439, 1833-1834.....	Leg	?	?	At birth 2 tumors running together; larger one size of "turkey egg." At 7 weeks involved entire leg. Became ulcerated. Amputated at 10 weeks. Infant died of infection. No microscopic study or necropsy
35	Birth	34 days	M	Peller: Wien. klin. Wchnschr. **35** : 126, 1922	?	?	?	In compilation of Austrian statistics says, "The youngest sarcoma patient was a 34 day old boy who was said by his parents to have been born with the tumor." No more information available
36	Birth	3 days	F	Pernet: Tr. Path. Soc. London **53** : 361, 1902	?	Subcutaneous lymph glands, muscles	Small round cell angiosarcoma	At birth 71 nodules, up to 1 × 3 cm. Lymph nodes enlarged. Eyeball protruding. Masses in calves and thighs No necropsy. Possibly neurogenic, as superficial growths followed cutaneous nerves

					glands, muscles	sarcoma	neurogenic, as superficial growths followed cutaneous nerves

37	Birth	?	?	Ramdohr: Virchows Arch. f. path. Anat. **73**: 459, 1878	Jaw ?	Subcutaneous, lung, kidneys	Angiosarcoma	Fatal hemorrhage from tumor on lower jaw. 22 subcutaneous tumors. Kidneys cystic and tumorous; little normal tissue remains. Metastases in lungs. Liver and adrenals not involved. A remarkable congenital malignant growth, but its nature cannot be determined from report
38	Birth	21 days	M	Ritter: Arch. f. klin. Chir. **5**: 338, 1864.....	Nose ?	Subcutaneous	?	At birth tumor larger than pigeon's egg hung from tip of nose, but spread in skin at base, and nodules were present in neck; grew rapidly. No necropsy. Called carcinoma (1864); more probably sarcoma
39	2½ months	4½ months	F	Rogatz: J. Pediat. **14**: 618, 1939.....	Thymus	Lungs, spleen, lymph glands	Lymphosarcoma	At 10 weeks enlargement of glands in neck noted, suggesting that the primary tumor of thymus may have arisen before birth
40	Birth	Birth	M	Rudd: Women's M. J. **10**: 93, 1900.....	Scalp	?	Fibrosarcoma	Tumor larger than head. No necropsy. Report inadequate. Case resembles Dardinski's
41	Birth	?	?	Schamoni: Ztschr. f. Krebsforsch. **22**: 24, 1924	?	?	?	In discussing cancer in young in Dortmund author mentions "one sarcoma in a newborn." No other information
42	Birth	?	?	Schuh: Pathologie und Therapie der Pseudoplasmen, Vienna, A. Braumüller, 1854, p. 245	Parotid ?	?	"Myxosarcoma"	Walnut size at birth. Size of man's fist at 5 mo. Report abstracted by Kaufmann (Arch. klin. Chir. **26**: 672, 1881). Malignancy doubtful. Outcome not given by Kaufmann. Original report not available
43	Birth	3 weeks	?	Stevenson: Brit. M. J. **1**: 9, 1876.....	Face	?	"Alveolar sarcoma"	Extended from front of ear along lower jaw to beyond midline. No necropsy. Called "large-celled alveolar sarcoma"
44	Birth	6 weeks	?	Winogradow: Med. Obozr., 1898; abstracted, Centralbl. f. Chir. **25**: 536, 1898	Skin	?	Angiosarcoma	Walnut size tumor on back at birth. Size of a child's head at 6 weeks. Original report not accessible
45	Birth	6 months' fetus	?	Zahn: Deutsche Ztschr. f. Chir. **22**: 287, 1885	Cheek	?	Myxosarcoma	Tumor, 15.5 × 12.5 cm., arose from sucking pad; contained areas of softening. May be myxolipoma but size suggests sarcoma
46	Birth	?	?	Zipkin: Virchows Arch. f. path. Anat. **186**: 240, 1906	Skin	?	Giant cell	Observed shortly after birth in left groin. Extirpated at 18 weeks when it was size of pigeon's egg. Contained giant cells of Langhans type

There are a few tumors reported as "myxosarcoma" at the umbilicus, without evidence of actual malignancy (Stoeckel; Cullen), which seem definitely to be merely benign hyperplasia of umbilical myxomatous tissue.

In addition to these published instances of congenital sarcoma, I have the privilege of mentioning a series of unpublished cases observed in his large experience during the past thirty-five years by Prof. Francis Harbitz, of Oslo, Norway, through his permission. As many of the growths were sent in for diagnosis from various places by practicing physicians, some of whom can no longer be reached, it is not possible to secure detailed information, especially in regard to the outcome. Professor Harbitz considers the following 13 cases to be certainly instances of congenital sarcoma.

1. Infant 3 hours old. Round cell sarcoma in elbow region, measuring 5 by 3.5 cm. Arm amputated.

2. Child 4 weeks old. Spindle cell sarcoma of right shoulder muscles. Shoulder disarticulation at 6 weeks.

3. Infant 8 days of age. Walnut-sized subcutaneous angiosarcoma.

4. Infant. Spindle and small round cell congenital sarcoma in region of nose.

5. Boy 3 months old. Congenital tumor, size of a pigeon's egg, under skin of neck, composed of round and spindle cells.

6. Boy 10 months old. Congenital round cell sarcoma on right arm, 7 by 9 by 12 cm. Shoulder disarticulation.

7. Girl 4 months old. Rapidly growing round cell sarcoma under skin of chest, observed some weeks previously.

8. Boy 4 months old. Tumor size of a hen's egg observed in occiput just after birth; vascular, polymorphous cell sarcoma.

9. Girl 6 months old. Congenital spindle cell and myxomatous sarcoma, very vascular, in neck and back.

10. Child 2 months old. Spindle cell sarcoma in mammary region, detected one month after birth, growing rapidly until "mandarin sized," with perforation of skin.

11. Boy 3 months old. Congenital spindle cell sarcoma in lip.

12. Boy 3 weeks old. Congenital angiosarcoma or endothelioma in subcutaneous tissue near trochanter.

13. Boy 2 years old. Congenital spindle cell sarcoma under skin of abdomen, in muscles.

While all these 13 tumors were congenital sarcoma in Dr. Harbitz' opinion, only in 4 cases (1, 3, 8, 12) is there information that the tumor was definitely present at or very soon after birth—although this may be implied also for those growths which are said to be congenital. In addition to the cases in the foregoing list, Professor Harbitz considers the following 9 cases to be probably instances of congenital sarcoma.

14. Boy 5 months old. Chestnut-sized sarcoma (fuso et grandicellulare) detected two months after birth in skin of back.

15. Child 9 months old. Spindle cell sarcoma in skin of nose.

16. Girl 2 years old. Giant and spindle cell sarcoma of mastoid bone, detected at 6 months.

17. Boy 4 months old. Small cell sarcoma of gluteal region, detected at 1 month.

18. Boy 11 months old. Small cell sarcoma of sacral region.

19. Boy 3 months old. Sarcoma in eyelid.

20. Child 4 months old. Spindle cell sarcoma, 6 by 4.5 cm., in parotid region.

21. Boy 4 years old. Large tumor on left heel, which had been observed at 6 months. This was a small cell sarcoma, which recurred after excision.

22. Boy 5 months old. Fibromyxosarcoma under tongue.

The fact that one pathologist, even although one with an exceptionally large experience, has seen sarcoma in so many young infants indicates that the number of published cases gives a very inadequate idea of the actual frequency of occurrence. At the time this paper was presented at the International Cancer Congress in Atlantic City, Sept. 11-18, 1939, several pathologists told me of unreported cases they have observed, indicating that the published reports do not begin to cover adequately the observed cases. Dr. Sidney Farber, who only a few weeks before wrote me that he had never seen congenital sarcoma in his large experience, was able to report a newly observed lesion of the arm of a newborn infant which was diagnosed as sarcoma.[6]

CONGENITALLY MALIGNANT (?) TERATOMA

In the older literature one finds that quite often teratoma is diagnosed as having sarcomatous or even carcinomatous elements. In table 10 are listed tumors that have been found cited as examples of congenitally malignant teratoma. It will be noted that most of the reports were published over fifty years ago, and few in the last twenty-five years. In only 1 instance was metastasis found, to confirm the diagnosis of malignancy, the instance reported by Frank from Chiari's laboratory. In view of the undifferentiated character of fetal tissues, especially the neurogenic elements, the actual malignancy of all the rest of this group may well be doubted.

In many cases teratoma presents such large accumulations of undifferentiated cells resembling malignant growths that it is difficult to know whether or not to accept the tumors as reported, i. e., as congenital malignant neoplasms, at least in the absence of metastasis or invasive growth, which usually is the case. The situation is made still more difficult by the fact that congenital teratoma may at any time in later

6. Since that date there has been published by Pack and Anglem (J. Pediat. **15**:372, 1939) the case of a female infant with congenital liposarcoma of the leg, cured (four years) by heavy radiation.

TABLE 10.—*Teratoma Reported as Malignant at Birth*

No.	Age When Seen	Age at Death	Sex	Author	Site	Metastases	Type	Comment
1	Birth	17 days	F	Braune: Monatschr. f. Geburtsh. **24**: 1, 1864	Sacral region	None	Mixed tumor, with sarcomatous elements	Size 10 × 9 × 7 cm. No good evidence of malignancy. Considered to be derived from coccygeal gland. Doubtful
2	Birth	Term	?	Dejerine and Hugonneau: Bull. Soc. anat. de Paris **51**: 290, 1876	Perineum	None	Small cell	Cystic, size of man's head. Reported as sarcoma but evidence of malignancy not adequate
3	Birth	8 months' fetus	F	Förster: Verhandl. d. phys.-med. Gesellsch. z. Würzburg **10**: 42, 1860	Sacral region	None	"Cystosarcoma"	Cystic spaces lined by epithelium; walls contained spindle cells and cartilage. No proof of malignancy
4	Birth	9 weeks	?	Frank: Prag. med. Wchnschr. **19**: 17, 1894	Sacral region	Local	Myxosarcoma	Metastases present in ischiorectal fossa. Diagnosed by Chiari
5	Birth	6 months' fetus	?	Gay: Boston M. & S. J. **63**: 402, 1860.....	Sacral region ?	None	"Encephaloid"	Three times size of head; caused dystocia. Cartilage, cyst and many cells
6	Birth	.....	..	Goldschmidt: Sacraltumoren und ihr Einfluss auf Schwangerschaft und Geburt, Inaug. Dissert., Berlin, G. Schade, 1896	Sacral region	None	Chondromyxolymphadenosarcoma	Size of child's head. Description of round cell masses does not establish malignancy. Cited by Hennig (below)
7	Birth	17 cm. fetus	M	Harbitz: Arch. Int. Med. **16**: 312, 1915.....	Sacral region	None	Neuroblastoma	7.5 × 6.5 × 3.5 cm. Contained cartilage and masses of undifferentiated nerve tissue; considered to be neuroblastoma. Perhaps resembled malignant tissue because so early in fetal life
8	Birth	7 months, fetus	M	Hennig: Beitr. z. path. Anat. u. z. allg. Path. **28**: 593, 1900	Sacral region	None	Myxosarcoma	Cystic teratoma with myxosarcomatous (?) ground substance. Chordoma, cartilage and epithelial cysts present. Not infiltrative
9	Birth	4 weeks	?	Mauthner: Arch. f. physiol. Heilk. **11**: 141, 1852	Sacral region	None	"Osteocystosarcoma"	Size of man's fist. Cysts lined with epithelium and filled with slimy fluid. Probably benign teratoma

10	Birth	3 months	F	McGiannan: J. Alumni A. Coll. Physicians & Surgeons **14**: 97, 1911	Ischiorectal fossa	?	Spindle cell sarcoma	Partial excision followed by death. Diagnosis: "Teratoma, small cell sarcoma." No further information obtainable
11	Birth	6 months' fetus	F	Neuffer: Med. Cor.-Bl. Württemb. ärztl. Ver. **44**: 83, 1873	Jaw	None	"Cystosarcoma"	Pedunculated growth, 13 × 9 × 5 cm., from left upper jaw. Called sarcoma, but no microscopic description given
12	Birth	Few days ?	?	Nissel: Virchows Arch. f. path. Anat. **269**: 446, 1928	Liver	None	Possibly sarcomatous	Contained cartilage, bone, epithelium and connective tissue elements; "apparently malignant" but not positively called sarcoma
13	Birth	Born dead	?	Ostermann: Monatschr. f. Geburtsh. **92**: 191, 1932	Liver	None	Resembling sarcoma	10 cm. in diameter, located in liver; consisted of cartilage, bone and many atypical elements, resembling sarcoma. Like Nissel's case
14	Birth	?	F	Rudolphy: Ein glandulärer maligner angeborener Sacraltumor, Thesis, Griefswald, J. Abel, 1897	Sacral region	None	Adenocarcinoma	Small at birth, grew rapidly and invaded sacral vicinity and gluteal muscles. Had glandular structure and thought to be carcinomatous. Cited by Hennig (above)
15	Birth	5 months' fetus	?	Sudhoff: Gynaek. Centralbl. **9**: 248, 1885...	Coccygeal gland	None	"Round cell sarcoma"	Contained also new formed striated muscle fibers and coccygeal gland elements. Evidence of malignancy questionable. Fetus edematous. Marked hydramnion
16	Birth	Birth	M	Tannahill: Glasgow M. J. **4**: 6, 1871.....	Thyroid	None	"Congenital tumor"	Larger than head of child. Examined by Joseph Coats, who found it "made up chiefly of round cells, also mucin, bone and cartilage"; does not call it sarcoma, as later authors have done
17	Birth	7 months' fetus	M	Zahn: Ztschr. f. Chir. **23**: 297, 1885.....	Thyroid	None	Chondro-osteoid sarcoma	Patient one of twin fetuses; the other normal. Tumor size of man's fist; described as "thyroidal chondro-osteoid sarcoma with embryonic striated muscle fibers and pigment cells"
18	Birth	6 months' fetus	?	Zeller: Thesis, Munich, 1892.....	Sacro-coccygeal region	None	"Adenocystochondrosarcoma"	Size of child's head. Largely cystic, lined with epithelium. No good evidence of malignancy

TABLE 11.—*Possibly Congenital Malignant Tumors of Undetermined Nature*

No.	Age When Seen	Age at Death	Sex	Author	Site	Metastases	Type	Comment
1	Birth	1 year	?	Clark: Brit. M. J. **1**: 418, 1883.....	Abdominal ?	Spleen ? testicle ?	Round cell sarcoma	Small swelling near femoral ring at birth; at 2-3 mo. involved testicle; at death involved most of peritoneal cavity, including spleen and testicle, but no other organs. Apparently congenital malignant growth but nature cannot be determined from report
2	Birth	?	?	Cotton: Prov. M. & S. J., 1849, p. 367.....	Arm	?	Carcinoma ?	Göbel cites this. Tumor on inner surface of left arm, removed at eighth week. Reported as carcinoma, but more likely sarcoma. Original report not available
3	Birth	Recovered	F	Dardinski and Delaney: Arch. Pediat. **53**: 659, 1936	Head	None	Cellular fibroma or fibrosarcoma	Premature infant weighing 4 lb. 11 oz. (2,126 Gm.). Tumor attached by pedicle in region of posterior fontanelle, weighing 495 Gm. Pedicle cut; no recurrence. Very cellular but no mitoses. I have seen sections and believe it to be an unusually cellular fibroma of infantile tissues
4	Birth	8 months' fetus	M	Dietrich: Verhandl. d. deutsch. path. Gesellsch. **14**: 353, 1910	Retroperitoneal	Pleura, heart, meninges, glands	"Lymphosarcoma"	Called retroperitoneal lymphosarcoma; site and spread suggest possibility of neuroblastoma, but kidneys, adrenals and liver were free
5	1 month ?	?	F	Dubreuilh: Ann. de dermat. et syph. **2**: 340, 1911	Skin	Axillary glands	?	Infant 7 mo. premature. Growth called sarcoma, although no microscopic examination. Considers it congenital, as at 1 mo. it was size of 50 centime piece. At 2½ mo. axillary glands involved. Described as pigmented like melanoma. No histoligic details. Very inadequate report
6	6 days	?	?	Günther: Ueber angeborene maligne Geschwülste, Thesis, Leipzig, 1923	Retroperitoneal	?	?	"Apple size tumor" compressing duodenum. Relieved by gastroenterostomy. Believed to be lymphosarcoma, although no biopsy, and outcome not stated. No histologic details. Very inadequate report
7	Birth	Recovered	F	Hess: Am. J. Dis. Child. **51**: 224, 1936.....	Thigh	None ?	Angiosarcoma	Roentgen examination showed bone destruction at 18 days. Aspirated fluid contained cells giving diagnosis of sarcoma, but no tissue sections made. Under roentgen therapy tumor disappeared, and no recurrence 2 yr. later, so malignancy not certain

8	Birth	?	F	Holmes: Tr. Path. Soc. London **14**: 248, 1873	Orbit ? eye ?	None	"Sarcoma" ?	Eye protruded at birth, and burst. Tumor was separable from bones of orbit and moved by eye muscles. Probably retinal neuroblastoma. "Removed successfully"
9	Birth	?	?	Körte: Deutsche med. Wchnschr. **18**: 572, 1892	Arm and scapula	?	?	Brief abstract of society meeting in which it is said there was a large tumor, which was believed to be an intrauterine developement of chondroma or sarcoma. No microscopic examination. No more information available
10	Birth	Soon	?	Ramdohr: Virchows Arch. f. path. Anat. **73**: 459, 1878	Lower jaw ?	Subcutaneous, lung, kidneys, abdomen	Angiosarcoma	Huge tumor of lower jaw, with many metastases. Undoubtedly congenital malignant neoplasm, but nature uncertain. Illustrations suggest chondrosarcoma
11	Birth	Recovered	F	Shore: Am. J. Cancer **27**: 736, 1936.....	Interscapular	None	Fibrosarcoma	Tumor removed at 2½ mo., diagnosed as fibrosarcoma by Thibaudeau. Recurred in 2 weeks. Partly removed at 6 mo., and diagnosed as fibrosarcoma, possibly neurogenic, by L. C. Knox. Grew for a few months and then disappeared without treatment and no recurrence in 7 yr.
12	Birth	?	?	Weinlechner: Arztl. Ber. d. Priv.-Heilanst. d. Dr. A. Eder **7**: 87, 1886	Parotid	Sternocleidomastoid	"Sarcoma" ?	Author stated by Heinecke (Ergebn. d. Chir. u. Orthop. **6**: 329, 1930) to have seen this child at 1 year, the tumors having been present since birth. Original article not available
13	5 days	16 days	?	Widerhöfer: Jahrb. f. Kinderh. **2**: 191, 1859	Generalized	Many	?	General Krebsdyskrasia—pinhead size nodules in nearly all viscera, especially liver and lymph nodes. Round cells with a tendency to shrink (Wedl). May be lymphosarcoma or neuroblastoma or leukemia
14	Birth	3 years	F	Williams: Lancet **1**: 1194, 1897.....	Vagina	?	?	In discussing cancer in young, author mentions case in which vaginal sarcoma present at birth was removed and recurred twice. (Recorded in St. Bartholomew's Hospital: A Descriptive Catalogue of the Anatomical and Pathological Museum, London, J. & A. Churchill, 1862, vol. 3, p. 156)
15	Birth	?	?	Winogradow: Med. obozr., 1898; abstracted, Centralbl. f. Chir. **25**: 536, 1898	Neck	?	Small round cell	Abstract merely mentions, among tumors seen at birth in 3,000 autopsies, an "81 Gm. small round cell sarcoma of neck." Original not available

life exhibit malignant development. Who can say whether the malignancy was present before birth or set in later? Early writers were inclined to report as instances of malignant teratoma those cases in which the microscope revealed considerable areas of undifferentiated tissues. Many of those were reported before the days of tissue staining, and a few in modern times.

Very puzzling is the case reported by Harbitz (1915) of a male fetus but 17 cm. long, approximately four months of development, with a huge sacral teratoma (7.25 by 6.5 by 3.5), which consisted chiefly of "embryonic, proliferating, not yet differentiated, nerve substance." He concluded that "the microscopic structure corresponded in every detail with the structure of neuroblastoma, and the tumor should be classified as such." The opinion of so competent a pathologist as Harbitz must be granted great weight, but is it not possible, or even probable, that had the fetus gone on to term the undifferentiated nerve elements would have gone on to greater differentiation and the teratoma then been classed as benign teratoma with a preponderance of nerve tissue elements?

CONGENITAL MALIGNANT TUMORS OF UNCERTAIN CHARACTER

In table 11 are listed a miscellaneous lot of what may well be congenital malignant tumors though their nature cannot be considered as fully established by the evidence available. The one reported by Dardinski and Delaney is particularly difficult. The tumor had reached enormous size at birth but did not recur after mere cutting through the pedicle. Dr. Dardinski sent me sections of the tumor, and I fully appreciate his caution in diagnosing the growth merely as a "tumor." It is so cellular as to suggest sarcoma, but mitoses are absent, and the cells are not markedly anaplastic. It may well be that this is fibroma, unusually cellular because the tissue is all so young, but I have seen growths that looked as innocent which produced metastases. The tumor reported by Rudd resembled this one closely in gross appearance, but there is no adequate histologic description of the growth, which was diagnosed as "fibrosarcoma."

In this group is the remarkable congenital tumor reported by Shore. It was removed at 2½ months and diagnosed as fibrosarcoma by a competent pathologist. It recurred promptly, and at 6 months a part of the large recurring tumor was removed and diagnosed as fibrosarcoma, possibly neurogenic, by another experienced pathologist. Despite the incomplete removal and some further growth, the tumor disappeared by the second year without any treatment whatever, there being no recurrence seven years later.

Among other tumors which have been recorded or cited as congenital sarcoma, but which cannot be accepted, are the following:

Stübinger, in 1903, cited a case reported by Bourneville and Bricon of a malformed child who died at the sixth day with a tumor, diagnosed as fibro-

sarcoma, involving the entire left side of the pelvis and the lateral and posterior surface of the thigh, but the reference given is incorrect and the original report cannot be located.

A case reported by Horn in 1864 appears in some compilations as one of congenital sarcoma of the large intestine, but in the original article it is said that the child was born sound, and the age when the tumor was observed is not stated, although the child by then had had measles and had been eating cherries!

Among other cases often cited in reviews of congenital sarcoma is that reported by Demme (1881) of a 5½ year old girl with fibrosarcoma of the vagina, which had been present as a pea-sized nodule since birth. Equally dubious as an instance of congenital malignancy is the case reported by Eröss (1883). A hard pea-sized nodule on the toe, present at birth, had scarcely increased in size when removed at 16 months and diagnosed as spindle cell sarcoma. This case was cited by Steffen with an incorrect reference, so that it cannot be subjected to critical consideration.

Hecker, in 1928, reported a case of spindle cell sarcoma. The tumor was cherry sized when noted in the buttock at 12 weeks. As it then doubled in size in fourteen days, the congenital malignancy is very questionable. Even more doubtful is the case reported by Lattes (1927) of multiple subctuaneous sarcoma, first observed at the third month, and a somewhat similar case with four nodules noted in the fourteenth week, reported by Odstrčil (1912). Also doubtful as sarcoma is the tumor of a 10 month old boy reported by Rapok (1890), first observed in the right ear at the tenth week. Göbel, in 1908, cited Walter as having reported a fist-sized tumor of the orbit, diagnosed as round cell sarcoma, in a deadborn fetus, but the reference given is not correct, and the original article cannot be found. In 1873 Schimdt's Jahrbücher abstracted a report on a series of tumors observed by Hofmokl and Albert, among which was a "congenital" walnut-sized myxosarcoma on the side of the knee of a 5 month old child, but as the original article is not available it is impossible to determine whether this tumor was present at birth.

A few borderline congenital tumors have also been reported, such as the so-called congenital epulis of the jaws and mouth, which is essentially benign, although sometimes becoming malignant. Abrikossoff expressed the belief that it was a myeloblastomyoma derived from abnormally located muscle tissue (see also Das). Wood, in 1904, reported a mixed tumor of the parotid, noticed in a girl soon after birth, which when removed at 7 months had grown to 7 by 4 cm. and which three years later had not recurred.

Although that rare tumor of the vagina, malignant rhabdomyoma, is found almost only in infants, it seems not to have been observed at birth. In their review Miller and Gurd (1910) stated that Wilms had reported a case in which this condition existed at birth, but gave no reference, and I have been unable to locate this report in Wilms' writings.

Lönnberg, in 1899, reported as sarcomatous a congenital cyst of the ovary which ruptured during delivery, but in his report I can find no evidence that there was any form of malignant growth.

A most spectacular congenital tumor was that reported by Ramdohr (1878). There was a huge tumor on the lower jaw, from which fatal hemorrhage occurred shortly after birth. There were 22 subcutaneous growths, as well as growths in the lung, thoracic and abdominal cavities, and both kidneys were cystic and tumorous. While this tumor is often included in lists of congenital renal tumors, there is nothing about the distribution and histologic picture to

suggest nephroma. The great tumor of the lower jaw most probably was the primary tumor, and the illustrations suggest chondrosarcoma, although it was reported as congenital multiple angiosarcoma. There can be no doubt that this was a genuine widespread congenital malignant neoplasm, but what kind?

CONGENITAL CARCINOMA

In contrast to the considerable number of cases of sarcoma actually, probably or possibly present at birth, is the scarcity of those of carcinoma of congenital origin. To be sure not a few cases have been recorded as cases of congenital carcinoma, and often cited as such, but most of them will not stand critical consideration. As stated previously, the several tumors which have been reported as congenital carcinoma of the liver must nearly all be discredited as erroneously diagnosed or as not established as present at birth. Most of the other tumors reported as congenital carcinoma were also diagnosed many years ago, when the differentiation of neoplasms was so little established that not much credence can be given to the terms used.

Among the most quoted of the reports is one of a supposed case of carcinoma of the stomach, presented by Cullingworth at the meeting of a society in 1877 and published only in an abstract of the proceedings. The lesion was observed in a boy who died at 5 weeks, having been ill since the ninth day of life with vomiting. The wall of the pylorus was ⅓ inch (0.85 cm.) in thickness. "A small pear-shaped tumor, 1 inch in length, sprang from the inner surface of the lower border of the pylorus. It was softened and ulcerated at the center and completely closed the pyloric orifice." Dr. Drechsfield "reported that the tumor was a cylinder-celled epithelioma, and that there was enormous hypertrophy of the muscular coat of the stomach in the neighborhood." No more detailed report was made. Ewing considered this to have been congenital adenoma of the pylorus, which seems much more probable than that it was truly malignant. In not a few cases, congenital pyloric hypertrophy has been reported as carcinoma, or at least as a gastric tumor, in the older literature.

The only cases that seem to be possibly instances of congenital carcinoma that I have been able to find are the following:

1. Frank, Enfield and Miller (1936). A newborn boy had a tumor of the tongue about the size of a pea. Biopsy showed it to be typical squamous cell carcinoma. At 2 weeks, when it measured 10 mm. in length and 6 mm. in width, it was removed. The illustrations seem to leave little doubt that it was truly squamous cell carcinoma, invading the underlying muscle. The regional lymph nodes were given roentgen treatment, although not enlarged, and two years later there had been no recurrence.

2. Anzilotte (1933). A neoplasm was present on the upper lip of a girl at birth. It grew progressively, became ulcerated and at two months occupied most

of the lip. The Wassermann reaction was negative. Biopsy showed typical squamous cell carcinoma, corroborated by adequate illustrations. Under irradiation the growth disappeared completely and did not recur during the next three years.

These 2 tumors seem, on the basis of histologic appearance, to have been typical squamous cell carcinoma but the final proof of metastasis, or even of recurrence, is lacking, and since it appears that in no other case has typical congenital carcinoma ever been reported, their malignant character cannot be considered to have been completely established in the absence of metastases or recurrence.

I am particularly inclined to be skeptical about these 2 tumors because of a third which was seen in our own clinic. A 13 month old girl with amaurotic family idiocy had a growth on the under surface of the tongue near the frenum. It was a cauliflower-like tumor, flat-elevated, about 1 cm. across, with a somewhat ulcerated surface. A biopsy section was diagnosed as squamous cell carcinoma by a competent surgical pathologist and by an experienced dermatologist, and the growth was removed by operation. Sections through the removed tumor showed granuloma with marked hyperplasia of the overlying epithelium. If, instead of operation, this child had been treated by radiation, the case would have gone on record as one of squamous cell carcinoma in a 13 month old infant.

Two cases of congenital thymic tumor have been reported as instances of carcinoma.

3. Bedford (1930). A full term boy showed many lesions of the skin at birth, which resembled pustules but contained no bacteria The Wassermann test was negative for both mother and child. There was an enlarged area of substernal dulness, and after each feeding there was cyanosis. The child died at 18 days, and necropsy revealed a thymus tumor with metastases to the bones, skin and liver but not to the other organs. The microscopic diagnosis of thymic carcinoma was confirmed by Broders.

4. Wasserman and Epstein (1939). This case is similar to case 3. A full term boy was born with a cutaneous eruption all over the body. As the mother had congenital syphilis, this was thought to be possibly third generation syphilis. The infant died at 7 days, and was found to have a tumor of the thymus with metastases to the lung, liver, spleen, pancreas, intestine, lymph nodes, skin, brain and bone marrow. The cells were very undifferentiated. James Ewing considered it to be probably thymic carcinoma but did not make a positive diagnosis.

But few other cases have been reported as instances of congenital carcinoma, none being satisfactorily established.

Ahlfeld, in 1880, reported a deadborn, deformed full term fetus (siren malformation) lacking kidneys, ureter and bladder. The large intestine ended blindly. At its lower end was a "mulberry-sized" mass diagnosed as cylindric cell carcinoma, without any evidence to support this improbable diagnosis. Probably the mass was merely the undeveloped end of the bowel.

In 1891 Bornemann reported the case of a boy who died of diphtheria when 18 months old but who had had stridor since the sixth week because of papillomatous growths in the larynx. These had recurred after operation. Although this case has sometimes been cited as one of congenital cancer of the larynx, there is no proof that these papillomas were either congenital or malignant, nor did Bornemann discuss the possibility of malignancy.

Blanc, in 1917, reported that in one year he had encountered 2 infants with mammary cancer. One was a boy. The mamma had begun to enlarge soon after birth, and at the age of 6 months the cancer had invaded the entire mamma and the glands in the axilla, but there was no ulceration, and the growth was not adherent to the pectoralis muscle. Blanc excised the mamma, the pectoralis muscle and the contents of the axilla. Three months later the child died from recurring hemoptysis. In the other infant the cancer developed in the same way soon after birth and in a few months spread to the axilla and into the hypochondrium. It was inoperable when he first saw the child. That one man should see the only 2 cases of congenital, or even infantile, mammary cancer ever recorded, arouses skepticism. The original article gives no illustrations. Apparently one of the growths was not examined microscopically, and the description of the limited study made of the other does not carry conviction that this really was congenital carcinoma of the mammary gland.

There are many references to a case of congenital carcinoma reported by Kaulich in 1864, but he merely said, "In the Archives de la société medicale d'observation" (no date) "is reported a case of colloid cancer of almost all the abdominal organs, including the skin, in a child 1½ years old," a statement which is far from convincing as to the occurrence of congenital carcinoma.

Schamoni (1924), in a review of cancers seen in Schridde's institute in Dortmund, Germany, mentioned that in 1917 carcinoma was observed in a newborn infant, but gave no further information. Letters to Dortmund elicited no reply.

A few cases of what was considered to be carcinoma in the very young may be mentioned, although none of them was probably an instance of congenital carcinoma.

In 1896 Selberg reported the case of a boy whose mother noted a red spot on the shoulder at 4 weeks, which was removed as a walnut-sized ulcerated tumor at 5 months, without recurrence. The microscopic diagnosis was "cancroid," so the congenital development and malignant character are both doubtful.

Körbler, in 1938, reported the case of a 3 month old boy, born with a hemangioma of the face, which became ulcerated. The diagnosis made by Saltykow on a biopsy preparation was "carcinoma planocellulare corneum." The lesion was treated with radium and apparently healed, but the child died some months later of "general weakness." There is no information as to recurrence or glandular involvement. This tumor can scarcely be considered as proved congenital carcinoma.

Herold, in 1933, reported carcinoma of the vagina observed in an infant at 3½ months, but there is no evidence that the cancer was congenital.

Dr. J. W. S. Blacklock, of Glasgow, Scotland, who has seen many tumors in young infants, writes me that he has seen "one malignant tumor in the ovary of a child of 2 months, and from the history it appeared to have been present at birth, as the abdomen was noted to be swollen. The tumor had the characters of a rather cellular carcinoma, but was well contained within the ovarian capsule

and had not spread to any other tissue. It may, of course, quite well have been of teratomatous origin, but though I investigated many portions of the tumor I could find no evidence of this."

Litten, in discussing sarcoma of the pancreas, in 1880, wrote, "many years ago Berg described a case of total carcinomatous degeneration of the pancreas in a newborn infant. This is the only case I can find." As Litten gave no referance and Berg's report cannot be located, this case must be considered dubious. Likewise a reference by Philipp to a case of carcinoma of the neck in a newborn infant, reported by Korte, is an incorrect reference, and the case report cannot be found for verification.

Hutchinson, in 1913, reported as multiple primary "carcinoids" growths in the skin of the left temporal region, first observed at 5 days, with many other growths appearing up to the time the patient was seen by the author, at 4½ years. The subsequent history is not given, and from the published report the nature is doubtful. The growths appear to have been too vascular to fit the diagnosis of carcinoid, and the dermatologists I have consulted are also uncertain as to whether this was a malignant tumor or not. Hutchinson said it was clinically benign.

Summarizing the cases of congenital carcinoma we find left only the following meager array:

Two cases of possible carcinoma of the mouth and tongue, not fully established.

Two or three possible but not completely proved cases of carcinoma of the liver.

Two cases of what was diagnosed as carcinoma of the thymus with more or less certainty (Ewing called his diagnosis a "guess").

A case of ovarian tumor histologically resembling carcinoma, but without infiltration or metastasis.

Two unverified cases of carcinoma of the breast reported by one observer.

A few unverified tumors in ancient literature.

Lacking more positive evidence, one may be justified in doubting that congenital carcinoma ever has been observed, and certainly none of the types common in adult life.

CONGENITAL GLIOMA

Despite the fact that peripheral neurogenic tumors are relatively frequently congenital and that glioma is often seen in young children, congenital glioma of the central nervous system is rare indeed. Bailey, Buchanan and Bucy, in their recent monograph on brain tumors in children mentioned no congenital tumors in their series, although 3 presented themselves in the first year.[7] They accepted the tumor observed by Canavan and Hemsath, which seems to me nothing more than a nest

7. The remarkable congenital papilloma of the choroid plexus recently reported by Drucker (Arch. Path. **28**:390, 1939) was one of the rare benign tumors in the newborn.

of undeveloped cells—"about 80 cells in the section," similar to the gliomatous malformations produced experimentally in the brains of chicks by von Szily.

Apparently cases of genuine congenital glioma of the brain are the following two:

1. Wollstein and Bartlett (1923). A male infant had "glioma sarcomatodes, of the left cerebral hemisphere, which was probably congenital, since symptoms were observed at 2 weeks, and death from a large tumor in the left cerebral hemisphere occurred at 8 weeks.

2. Russell and Ellis (1933). A cerebral glioma was observed on the left side in a full term stillborn girl. This tumor was 8.5 by 7.5 by 6 cm. and was diagnosed as "polar spongioblastoma."

Under the title "Encephalitis Congenita," Amolsch discussed the subependymal infiltration of small round cells found in the brains of newborn infants, these not being inflammatory but developmental foci. They are most pronounced between the eighteenth and twenty-eighth week of fetal development. Often a massive intraventricular hemorrhage comes from this tissue. He suggested that these foci may give rise to glioma in early childhood, but the tumors in early childhood are not often located in this part of the brain. He said, "In one of the cases where massive hemorrhage involved the region of the thalamus at birth, sections from this area reveal a tumorous growth of large cells with vesiculated nuclei in an excessively rich vascular bed, the entire picture being that of a glioblastoma." Dr. Amolsch informed me that the exact diagnosis in this case is uncertain, because it was observed long ago and only one poorly prepared slide was available when he wrote on the subject. This section has been examined by Dr. Percival Bailey, and he agrees with Dr. Amolsch that the section warrants the diagnosis of glioblastoma.

Breitenborn cited Maier (1861) as having reported glioma of the lateral ventricle in a 10 week old infant, but the original report is of teratoma, containing bone, cartilage, skin and hair, and not a suggestion of glioma.

Braune, in 1937, reported 3 brain tumors in infancy, one of which may have been congenital glioma, as at 14 weeks there was a large cellular tumor, diagnosed glioma, in the left cerebral hemisphere (approximately 4 by 4 by 8 cm. to judge from the photograph). However, no symptoms were noted until the day before death.

According to Steffen (1905), Dotzauer reported what might be dural "endothelioma" or meningioma in a newborn boy. The growth extended from the dura in the vicinity of the occipital protuberance, penetrating the occiput but not involving the brain. Unfortunately, the reference given by Steffen is incorrect, and the original article cannot be found.

A large tumor found in the left cerebral hemisphere of a girl dying on the second day of life was diagnosed as angiosarcoma by Corten (1921).

CONGENITAL ENDOTHELIOMA

In addition to the hepatic vascular tumors a few other congenital neoplasms have been reported as endothelioma in early infancy, possibly congenital. Recognizing that all diagnoses of endothelioma are difficult, I find the most probable of the reported cases are the following:

1. Stapel (1937). A boy was born with a tumor the size of a walnut on the left side of the neck, which in two weeks was the size of a man's fist and threatened asphyxia. It was then removed incompletely, being adherent to the trachea. Recurrence was prompt, with death three weeks later, when the tumor was the size of a hen's egg and compressed the larynx. The thyroid and thymus were not involved, but the site of origin could not be determined. There were no metastases. The diagnosis was "malignant endothelioma."

2. Dordick (1938). An Italian boy had a pigmented tumor on the back which was partially "amputated" traumatically during birth. It grew rapidly, and at 5 months a pedunculated tumor 9 cm. in diameter was removed for biopsy and diagnosed hemangioendothelioma. At death, occurring at 7 months, there were several cutaneous lesions, the liver was enormously enlarged, and there was a large mass in the left upper quadrant of the abdomen, but unfortunately no necropsy could be made, so the nature of the internal tumors is not known. Doubt is thrown on this case by the fact that the cutaneous lesions did not change in size or appearance, and the photomicrographs do not seem to be those of a malignant tumor. Since endothelioma does not often metastasize widely, the large mass in the left upper quadrant of the abdomen, together with a rapidly enlarging liver, suggests the possibility that this is a case of malignant adrenal neuroblastoma with coincidental cutaneous hemangioma.

Wollstein, in 1931, reported a case of multiple hemangioendothelioma of invasive and malignant character, involving the right lung, intestine, pancreas, adrenal, scalp, abdominal sympathetic ganglions, lip and adipose tissue. The tumors were found in a girl with symptoms since the seventh or eighth week of life, when roentgen rays showed a pulmonary tumor. Death occurred at 4 months and 20 days, but the postmortem examination failed to reveal which was the primary growth, and the congenital nature, of course, is not established.

A rather similar case was reported by Taylor and Moore in 1933. A girl dying at 5 months had had cutaneous angiomas in the skin and labia since the third month. Similar tumors were found in the lung, liver and skin, and although the hepatic growth was invasive, the rest seemed benign, so the malignancy and congenital activity are both doubtful.

Still more doubtful as to malignancy is the case of multiple endothelioma of the skin reported by Dörffel (1929).

Jaffé, in 1929, reported the case of a girl with a huge hemangioma on the skin of the neck at birth and many minute ones (about 100)

elsewhere in the skin, who died of meningitis at about the eighth month. Necropsy revealed multiple hemangioma of the skin, leptomeninges, dura mater spinalis, diploe of the parietal bone, thyroid, lungs, intestines and spleen. He discussed the question as to whether these are true tumors (hemangioma) or angiectases. He looked on this case as one of hamartoma with a tendency toward continuous growth. There was no evidence of neoplastic endothelial hyperplasia, and the multiplicity was considered evidence not of metastasis but of simultaneous independent excessive vascular growth.

The growths in the case of hemangioendothelioma of the ileum in a 2 month old girl reported by Blahd, Mashke and Karsner (1923) were somewhat more cellular and apparently truly neoplasm, but without metastases or other evidence of malignancy beyond a slight local invasive property. They said, "From the age of the patient and the character of the tumor, it seems probable that the condition was congenital."

CONGENITAL MELANOMA

Although pigmented moles are frequently present at birth, they rarely become malignant before birth or even in infancy. The only case found in which malignancy may have been prenatal was reported by Coe in 1925. A girl at birth had two wartlike growths, "slightly larger than the head of a black pin," in the scalp in the left frontal region. They grew rapidly, so that at 2 months they formed a mass 1½ inches (3.5 cm.) long and 1 inch (2.5 cm.) high. A week later a swelling was found in the left side of the neck. At 3 months it was incompletely removed, and despite roentgen therapy, death occurred one month later. Unfortunately, necropsy was not performed. Microscopically, as well as clinically, it was malignant cutaneous melanoma.

Weinlechner said that Jablokoff and Klein, in 1879, reported the case of a girl who at birth "had innumerable gray-brown spots up to bean size over the entire body, besides diffuse pigmentation on the body. It died in the seventh month from tuberculosis. In the brain were found five nodules of melanosarcoma. (They might have been primary in the brain.)" I have been unable to see the original article, so cannot evaluate the scanty evidence. Nothing more is said in the abstract, so whether the retina was involved, or the liver, is unknown.

A tumor diagnosed as primary melanotic carcinoma of the adrenal by Chiari, who performed the necropsy, was reported by Reinmann in 1902. The infant was admitted to the hospital when 9 days old, being then icteric and suspected of having syphilis, which the mother had. When the child was 10 weeks old, a pea-sized nodule was noted in the subcutaneous tissues of the abdominal wall, and two weeks later nodules were found on the skull. These were not influenced by mercurial inunctions. The child died when 7 months old. Both adrenals were

found involved, with metastases in the abdominal and thoracic walls, bones, muscles, dura, liver, mammae and inguinal canal. Primary adrenal melanoma is extremely rare, but Chiari's opinion is entitled to great weight. However, whatever the nature of the growth there is no conclusive evidence that it was congenital, although most probably it was.

Dudits and Szabó, in 1935, reported *"melanocarcinoma congenitum processus alveolaris"* observed in a girl on the seventh day after birth. At first there was a pea-sized nodule on the upper jaw; it grew steadily, and at 5 weeks it was "nut-sized," [8] and from it a tooth protruded. At operation, at the sixth week, the tumor was found to be infiltrating the upper jawbone and spreading to below the orbit, so only part was removed. Under roentgen rays the growth receded, and at 2 months of age the child was in good health. Subsequent events are not recorded. Microscopically, the growth was described as "a pigmented carcinoma, which probably arose from the enamel organ." A similar case was reported by Krompecher (1918). A tumor the size of a hazelnut was observed in a 2 month old child, but nothing is said about when it was first observed, so its congenital nature is not established, even if one could accept the diagnosis of melanocarcinoma arising from an undeveloped tooth.

CONGENITAL MALIGNANT TUMORS OF THE TESTICLE

Occasionally the statement is found that the testicle is sometimes the seat of a congenital cancer, but actual proof of this is lacking. For example, Guersant (1873) in his "Surgical Pediatrics" said that he had seen at least 10 cases of testicular cancer in young persons, part in newborn infants, but he gave no specific reports. Von Pitha (1864) also said that he had seen a testicular *Markschwamm* (soft cancer) in a newborn infant, but did not give details. Presumably these early authors were discussing teratoma, which occasionally is present at birth. Such a tumor was reported in 1874 by Farrington, the enlargement having been noted at birth. At the end of the first year exploratory incision of the walnut-sized tumor was followed by progressive growth so that at the age of 17 months it was the size of a goose egg. Operative removal was followed by death two days later, but as there was no necropsy and apparently no microscopic study, the recorded diagnosis of carcinoma is far from established. Another supposed congenital carcinoma of the testicle reported by Clark (1900) is also doubtful. No enlargement was noted until the tenth week. At 8 months a tumor weighing 1 ounce (28 Gm.), was removed and diagnosed as columnar cell carcinoma. The outcome is not stated. No more recent reports

8. Whether hazelnut or coconut is not specified.

can be found indicating congenital or even early infantile malignant growth in the testicle, which makes all earlier reports even more doubtful.[9]

Since most testicular tumors arise in teratoma, probably many of these are present before birth, although the malignant process rarely begins before puberty. Of 100 malignant testicular tumors reviewed by Tanner (1922) only 1 occurred before the seventeenth year. In a review of malignant disease of the testicle (1926) Dew mentioned only 2 cases in infants. One had swelling at 3 months; orchidectomy was done at 12 months, and death occurred three months later, with pulmonary metastasis. The other tumor was first observed at 16 months. A typical case is that of Philipp, in which the testicle was enlarged at birth. Not until traumatized in the third year did it grow rapidly, and on removal, sarcomatous degeneration of a growth, diagnosed as teratoma, was found. MacLennan also reported a case in which enlargement of the testicle was present at birth, with resection at the eleventh month, followed by development of metastases in abdominal and cervical glands and death in two weeks. Histologically it was considered to be adenocarcinoma.

Gay, in 1860, said that he once saw in the testicle of a nursing child an "encephaloid disease," which appeared when the infant was 8 days old, and he referred to a specimen of this tissue in the collection of presumed congenital cancers of the Boston Society for Medical Improvement, described in their catalogue, page 43—where it could not be found. Equally impossible is verification of a case reported by Drew (1902), all the information available being mentioned in a brief account of a meeting of the Society for the Study of Disease in Children, in which it is said that "Dr. Douglas Drew exhibited a specimen and sections of an adenomyxosarcoma of the testis taken from an infant."

CONGENITAL CHORDOMA

Although chordoma is derived from persisting fetal tissue (notochord) and often is malignant, yet it rarely manifests itself before puberty, occurring mostly after the age of 40, as shown by the compilation of 150 cases by Mabrey (1935). The only congenital tumors of this type found by him were that reported by Hennig (1900) in a 7 month fetus, and one excised from the mouth of an infant 24 hours old by Rubaschow (1929), but the published reports do not indicate whether these growths were malignant or not. Hennig's growth seems to have

9. E. Sickmüller (Arch. f. Thierheilk. **63**:321, 1931) has reported as congenital carcinoma of the testicle in a calf a growth observed at birth and much increased in size at the fifth week, when necropsy revealed extensive peritoneal metastases.

been a mixed tumor, some parts of which were said to resemble myxosarcoma, some cartilage and some chorda dorsalis, but that there really was malignant growth is not established and is improbable from the description. Montgomery and Wolman (1933) reported 3 such tumors in infants, and as one of these, a girl, showed symptoms of obstruction at 2½ months, it is very possible that this tumor had been present since birth. This view was supported by the findings at operation at 3½ months, when the tumor was found to have invaded the bladder and the abdominal wall, so it was unquestionably malignant. Death occurred three weeks later. Permission for a necropsy was not obtained. There seems little doubt that this was truly congenitally malignant chordoma, although its prenatal malignancy cannot be proved.

CONGENITAL LEUKEMIA

In view of the frequent occurrence of leukemia in young children it is surprising to find almost no instances of congenital leukemia if one eliminates some cases reported as such which were undoubtedly cases of erythroblastosis. The difficulty in differentiating leukemia from erythroblastosis in the newborn is demonstrated in the case reported by Rhamy (1938) of a newborn infant who died from rupture of the spleen, for some who studied this case considered the condition to be erythroblastosis, and more believed it to be leukemia.

Büngeler (1931) accepted Koch's diagnosis of congenital myeloid leukemia in a full term fetus, and reported, with the same diagnosis, the case of a 7 month male fetus with leukemic blood, 80 per cent of the cells being myeloblasts and myelocytes. Stransky (1925) reported earlier a case of myeloid leukemia in a girl born with cutaneous leukemic infiltration, who died at 3 weeks with findings suggesting a chloromatous process; the blood contained 181,000 leukocytes, of which 86.1 per cent were myeloblasts.

Geschickter and Widenhorn (1934), in discussing their cases of benign renal cystadenoma, mentioned a case in which an infant died at 9½ hours of lymphoid leukemia. Branch (1933) reported as lymphoblastoma what may have been leukemia, but symptoms were not noted until the second month. No mention is made of blood counts, but it is said, "The larger vessels show such a preponderance of cells of the lymphocytic series that one is forced to believe that the white count would have been in the hundreds of thousands." The necropsy was very incomplete and so is the report.

Acute leukemia, whatever its relation to chronic leukemia and true neoplasms, certainly differs in being much more often seen in children, and in not a few cases it has been observed in the first weeks of life (Forkner). Cook, in reporting 50 cases of infantile leukemia, said, "In one the disease was congenital, the first symptoms being noted on

the fourth day of life; the baby died on the twenty-third day.[10] The observed onset of the second case was at the age of 10 days, and the baby lived three months. "These cases were typical clinically and had the characteristic blood picture."

Leukemia is readily transmitted from one animal to another, at least in the case of related mice and in fowls. It is therefore indeed surprising that leukemia in the pregnant woman is not often transmitted to the offspring, since leukemic cells seem able to invade tissues much as do malignant cells, yet I have been unable to learn of such a case by a review of the literature or by inquiry among experienced hematologists. For example, Zanela (1937) collected from the literature 41 cases of leukemia during pregnancy, added 2 cases of his own and stated that leukemia is not transmitted to the child.

An interesting observation is that reported by Russell (1933). He encountered chronic lymphatic leukemia complicating pregnancy. The infant, a boy, delivered three weeks prematurely, had at 6 weeks a very abnormal blood picture, namely: leukocytes, 17,100; lymphoblasts, 5; large lymphocytes, 21; small lymphocytes, 27; medium lymphocytes, 29; metamyelocytes (I), 2; metamyelocytes (II), 4; mature neutrophils, 10; eosinophils, 2. Dr. Russell writes me that two years later the child had a normal blood picture.[11]

INTRAUTERINE TRANSMISSION OF MALIGNANT GROWTHS FROM MOTHER TO FETUS

Intrauterine transmission of tumor is remarkably rare, there being found but 4 acceptable cases:

1. Friedreich (1866). A metastatic growth was observed in the skin of the knee in a male fetus, slightly premature, delivered three days before the death of its mother from generalized carcinomatosis, probably from bronchogenic carcinoma, although Friedreich thought it primary in the liver. There were no other metastases in the infant or in the cord or placenta.

2. Berghinz (1913). Miliary lymphosarcomatous metastases were found in the liver of a child born immediately before the death of the mother, who had lymphosarcoma of the cervical and axillary nodes, with hepatic metastases. Nothing is said as to whether the placenta was involved.

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10. This case of acute leukemia was reported in full by P. J. White and E. L. Burns (Am. J. Dis. Child. **41**:866, 1931). Another case of chronic myelogenous leukemia, well developed at the third month and hence perhaps congenital, was reported from the same clinic by Alvis (Am. J. Ophth. **21**:31, 1938).

11. Since the foregoing was written Morrison, Samwick and Rubinstein (Am. J. Dis. Child. **58**:332, 1939) have reported a case of congenital leukemic myeloblastosis with chloromatous areas and tabulated 27 cases reported as instances of congenital leukemia, of which, they say, "in only 7 in all probability was the involvement truly congenital."

3. Weber, Schwarz and Hellenschmied (1930). A child was born three months before the death of its mother from melanosarcoma, the placenta having been black with metastases. When 8 months old, the child was found to have an enlarged, nodular liver. It died at 10¼ months with subcutaneous nodules as well as the hepatic metastases.

4. Holland (1933). Extensive melanosarcoma metastasis was observed in the placenta of a woman delivered by cesarean section two months before her death. The primary melanoma had been excised from the skin of the thigh, but recurred. At the time of the operation the mother's peritoneum was found studded with metastases. The child seemed well for eight months but died at 10 months with generalized metastases.

Doubtful, chiefly because of inability to verify, is a fifth case, which Coroënne, in 1884, referred to as reported by Cornil, in which the child of a woman with cancer of the cervix uteri was found to have cancer of the thyroid, peritoneum, frontal bone and left patella. This was referred to by Danforth (1937), but I have been unable to locate either Coroënne's thesis or the original statement of Cornil for verification. Danforth commented on the fact that in a large series of statistics cancer of the cervix was shown to be present in 0.032 per cent of pregnancies without even placental involvement. Gray, Kenny and Sharpey-Schafer reported a case of metastasis to the uterus and placenta from an adrenal tumor, without metastases appearing in the child, who lived for six months and showed no tumors at necropsy. Other cases of metastasis to the placenta not involving the fetus have been reported by Walz (myxosarcoma), Markus (melanoma; no mention of examination of the fetus) and Senge (gastric carcinoma; 22 cm. fetus without metastases).

Priesel and Winkelbauer (1926) reported a case of lymphogranuloma in a child dying at 4½ months, the mother having died of the same disease a few weeks after delivery. Von Braitenberg (1938) reported as an instance of congenital lymphogranulomatosis a case in which the mother was not proved to have the disease, and some have thought this more likely a case of primary lymphoblastoma in the infant, which showed no lesions until 1 month old.

MALIGNANT PLACENTAL TUMORS

Placental tumors are essentially prenatal tumors of the fetus, but how many of the tumors diagnosed as chorionepithelioma began as malignant growths before term, and how many acquired malignant properties in residues left after delivery of the placenta, it is impossible to say. Davis and Brunschwig said, "It is true that many of these tumors first make themselves evident in the immediate postpartum period. Although it has been felt that they begin their growth at the termination of gestation and grow rapidly, it is entirely possible

that they begin their malignant growth during the latter part of the gestation." These authors reported a case of chorionepithelioma present at the time of delivery of a 6 month fetus, which lived one hour, and stated that this is the first instance of a tumor of this type being found with a living infant. As the mother had a pregnancy eighteen months previously, it is not possible to say whether the malignant growth came from placental elements left from the previous pregnancy or from the placenta accompanying the fetus, the latter being the more probable.

In many of the cases chorionepithelioma certainly seems to have arisen before the pregnancy was completed; for example, in the case of tubal pregnancy reported by Heuck and Hanser, the growth was found only six or seven weeks after menstruation had ceased. In one of the few cases of primary sarcoma of the placenta, that reported by Cary, the pregnancy was about two weeks short of full term at the time of discovery of the tumor; the mother and child were both well two years later.

Possibly chorionepithelioma is practically always to be looked on as a prenatal malignant growth, for Ewing said that "destructive mole usually yields symptoms between 4 and 5 months after the last menstruation." Perhaps this may be explained on the basis of the fact that the placenta is an organ of remarkably short life cycle, being developed *ab ovo,* maturing, and becoming senile in six to seven months. As Warthin (1929) said, "All of the involutionary tissue changes of old age appear in this important vascular organ at the completion of the period of intrauterine life. In the fulfillment of its function the placenta passes through well defined stages of evolution, maturing and senescence, and when its work is over it is discarded as useless and disappears from the scene of the individual life. Prophetic of the future fate of the organism as a whole!" If, like other organisms, the placenta requires one sixth to one tenth of its life cycle to produce carcinoma, a very few weeks should be adequate for the production of chorionepithelioma. Furthermore, in possession of invasive properties whereby they penetrate into blood vessels, placental cells are endowed from the start with a major attribute of malignancy.

GENERAL CONSIDERATIONS

An unexpected feature in the reports studied in making this review is the lack of evidence or suspicion of hereditary influence except with the retinal tumors. With few exceptions, the authors mention the absence of familial malignancy, for the surprising occurrence of cancer in a newborn infant naturally invites investigation as to possible inheritance. Schnorbusch and Kujath, in considering cases of carcinoma in the young (under 35 years), made an investigation of the families and found no unusual mortality from cancer among the relatives.

There were found among the cases accepted in this paper as actually or at least possibly cases of congenital malignant neoplasm, the following cases in twins.

1. Amberg (1904). Neuroblastoma of the adrenal was found in one of twins at 2 months. Whether these were identical twins, and whether a tumor developed in the other twin, is not stated or now known by Dr. Amberg (personal communication).

2. Rostkowski (1932). A sister twin had what was probably neuroblastoma of the adrenal. A brother twin was well (how much later is not stated in available abstract).

3. Taillens (1930). One of twin boys (not stated whether identical) had liver cell carcinoma, with death at 6 months. The other twin was well one month later.

TABLE 12.—*Summary of Recorded Congenitally Malignant Tumors (Not Including Retinal Tumors)*

	Accepted	Probable	Possible	Total
Malignant renal tumors	5	11	?	16
Malignant adrenal neuroblastoma	17	15	21	53
Malignant extra-adrenal neuroblastoma	6	4	?	10
Congenital sarcoma	33	29	53	115
Teratoma; malignant at birth	1	2	?	3
Tumors of undetermined nature	3	1	7	11
Carcinoma of liver	0	1	9	10
Malignant hemangioendothelioma of liver	?	?	15	15
Hepatic tumors of undetermined character	?	?	4	4
Carcinoma, excluding liver	0	0	5	5
Cerebral glioma	1	1	2	4
Malignant endothelioma, excluding liver	?	?	5	5
Melanoma malignum	0	2	2	4
	66	66	123	255

4. Veeder and Austin (1912). One of twin girls (not stated whether identical) had congenital hemangioendothelioma of the liver. The history of the surviving twin is not given and not now known by either Dr. Veeder or Dr. Austin (personal communications).

A summary of all congenital malignant growths found recorded in a thorough search of the literature, which of course does not succeed in finding all published reports of such tumors, is given in table 12. From this are omitted retinal tumors, 7 per cent of which are said to be demonstrably present at birth, and all of which may be at least potentially malignant cell aggregates at or before birth. Included are the 22 tumors diagnosed as sarcoma by Harbitz and not listed in the tabulation of sarcoma.

This table brings out certain facts of significance, perhaps the most striking of which is that sarcoma is practically the only malignant tumor common in adult life which is likely to be present at birth, the other two major groups, carcinoma and glioma, being almost unknown in newborn infants. Not a single example of carcinoma of the alimentary

canal, lung or genitalia, which are the commonest of malignant growths, has ever been convincingly reported as observed in a newborn infant. Why should sarcoma be so much more frequent in the very young than carcinoma? Until the days of experimental carcinogenesis there was a strong suspicion that sarcoma and carcinoma might have distinctly different etiologic factors. But it was soon found that the same cancerigenic agent might produce equally well sarcoma or carcinoma, the type depending more on the tissue to which the agent was applied or the species of animal used than on the agent. The other factor in the production of tumors, heredity, seems to have a similar influence in producing either carcinoma or sarcoma. While mice usually show carcinoma rather than sarcoma, Maud Slye has strains in which sarcoma rather than carcinoma develops; and lymphosarcoma and related lymphocytic overgrowths have been found to appear predominantly in certain strains of mice. From the statistical evidence it might appear that the agents inciting sarcoma formation act more quickly than those responsible for carcinoma formation, since sarcoma so often appears in early life,[12] but in experimental cancerigenesis it seems to require about the same length of time to produce sarcoma as carcinoma in animals of the same species. The bone sarcoma produced by radium, as reported by Martland, with few exceptions appeared ten to sixteen years after the exposure to radium, just as does carcinoma of the bladder in dye workers and carcinoma of the skin from roentgen ray exposure. Furthermore, the age peak of sarcoma incidence is not much earlier than that of carcinoma incidence (Weller; Schamoni). This might suggest that sarcoma of infants is in some way different from sarcoma of adults, but nothing can be found in the approximately hundred cases of sarcoma of the newborn described in this compilation that seems to suggest any striking difference. The sarcomatous growths attack the same sites, grow the same way and seem to be not noticeably different in malignancy from growths of similar structure in adults.

Apparently bone growths constitute a smaller proportion of the group diagnosed as sarcoma than in adults, for but 22 tumors in this group were definitely indicated as arising in bone, although 16 were said to arise in an extremity or a shoulder without its being clearly indicated whether they arose in bone or soft tissues. Therefore apparently about 75 to 80 per cent were sarcoma of soft parts, instead of the usual 50 to 60 per cent of most statistics on sarcoma. But this difference indicates no obvious difference in the causes of sarcoma at birth and later.

12. Twenty-six and seven-tenths per cent of cases of sarcoma in patients below 25 years, as compared with 1.2 per cent of carcinoma in the statistics of Pack and LeFevre (J. Cancer Research **14**:167, 1930).

On the other hand, the rare tumors which appear almost exclusively in childhood and seldom after puberty, namely, retinoblastoma, neuroblastoma of the adrenal and sympathetic system (sympatheticoblastoma), malignant mixed renal tumors and the progressive hemangioendothelioma of the liver (which is of doubtful malignancy), constitute together about as many congenital malignant tumors as does sarcoma, although but a few hundred such tumors have been observed at all ages. At least in the case of sympatheticoblastoma, retinoblastoma and malignant nephroma one is dealing with malignant growths which arise from incompletely developed fetal structures, which apparently go on to malignant growth either early or not at all. There is evidence, at least in the case of sympatheticoblastoma, that the embryonal malformations which do not kill as malignant growths may either disappear without forming tumors, or may form benign tumors, or may form transitory progressive growths which may revert to benign growths (ganglioneuroma), or perhaps disappear entirely, like the embryonic malformations which never assumed neoplastic character. There is some evidence that the same is true of retinal growths, and since nephroma arises from a fetal tissue that vanishes at about the time of birth, its presence in early life and absence in later years may depend on a similar property. There is no evidence that heredity plays any role in the occurrence of either malignant nephroma or sympatheticoblastoma, whereas there is no other form of malignant neoplasm in which heredity plays so evident a role as in retinoblastoma, which is strikingly familial. For this discrepancy no explanation is apparent as yet.

For this group of infantile neoplasms no long-acting etiologic agent seems to be required, as for most forms of cancer. Some of the latter seem to depend on hormonal influences, which might conceivably act in utero, as contrasted with some other forms of cancerigenic agent, but there is no apparent evidence that endocrine factors are of significance, and no explanation of why prenatal growth factors should produce malignant growth in certain growing tissues and not in any of the rest of the actively growing tissues. As Ballantyne pointed out, the fetus itself at about the fifth month is a most remarkable neoplasm, quadrupling its weight in a month.

Faerber made some interesting and suggestive observations concerning the neoplasms of early life, concluding his paper with the following pertinent remarks:

> Cramer has directed attention to the fact that the retinoblastoma, which appears almost exclusively in infants, and the chorion-epithelioma, arise from tissues that have a type of metabolism resembling that of tumours.
>
> Besides the retinoblastoma, the neuroblastoma and nephroblastoma are also tumours of the first few years of life, and in recent years it has been shown that brain and kidney medulla have a high glycolysis. Thus these tissues also have a metabolism resembling that of embryo and of tumour, and this may have some

connexion with the occurrence of these tumors in the early years of life. Whether the nephroblastoma arises from the medulla of the kidney is doubtful, but in my opinion these relations are of the utmost importance and should be borne in mind by pathologists and workers who hope to unravel the causative mechanism of cancer.

It is irrational to work on the hypothesis that cancer afflicts cells and tissues of all ages through the same mechanism, when the cancers of infancy may constitute a separate category by virtue of the peculiar metabolic properties of the tissues of their origin.

SUMMARY

In about 3,000 necropsies on newborn infants, including many premature fetuses, 4 congenital malignant neoplasms were found, all neuroblastoma, 3 in the adrenal and 1 involving much of the sympathetic nervous system.

A critical analysis has been made of the literature to determine the occurrence and significance of malignant tumors present at or before birth. The existing compilations are full of errors from failure to consult and evaluate the original reports, many of which are in ancient literature. There have been found in all about 250 reported neoplasms that were certainly, probably or possibly truly malignant growths present at birth, but of these only 66 can be considered as established beyond possible doubt.

While sarcoma constitutes nearly one half of these tumors, yet there are nearly as many instances of neuroblastoma established as congenital as of sarcoma, and a vastly larger proportion of all recorded neuroblastoma was present at birth, as compared with the relatively small proportion of sarcoma present at birth.

Not a single case of congenital carcinoma can be found convincingly established, although several possible cases are reported, especially cases of carcinoma of the liver. There is no example of congenital occurrence of the common types of carcinoma, namely, of the alimentary canal, lung and genitalia.

Evidence is found that congenital maldevelopments of nerve tissues occur frequently, and these apparently may disappear, develop into malignant tumors, develop into benign tumors or even become malignant and then change in whole or in part into nonmalignant tissues.

While a large proportion of all neurogenic malignant tumors derived from the sympathetic nervous system and from the retina are present at birth, congenital neoplasms of the brain and peripheral nerves are extremely rare.

In striking contrast to retinoblastoma in which the hereditary factor is marked, the other types of tumors that tend to be congenital or to appear in early infancy show no apparent familial or hereditary influence.

Some cases of true congenital leukemia have been reported, but not a single instance has been found in which leukemia has been trans-

mitted from mother to fetus, although there are a few instances of metastasis of maternal cancer to the fetus.

The significance of congenital malignant growth is discussed in the light of the fact that ordinarily a large part of the life cycle is required to produce any type of malignant tumor.

Presumably the malignant growths which appear chiefly before or soon after birth depend on some other mechanism or principle than the ordinary malignant growths that require so long for their production. Cramer directs attention to the fact that the retinoblastoma, which appears almost exclusively in infants, and chorionepithelioma, arise from tissues that have a type of metabolism resembling that of tumors. Besides retinoblastoma, neuroblastoma and nephroblastoma are also tumors of the first few years of life, and in recent years it has been shown that brain and renal medulla have high glycolysis. Thus these tissues also have a metabolism resembling that of embryo and of tumor, and this may have some connection with the occurrence of these tumors in the early years of life.

(References for cases listed in the tables are given therein and not repeated here unless referred to in the text.)

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Case Reports

DYSTROPHIC CALCIFICATION OF THE MYOCARDIUM WITH GLOMERULONEPHRITIS

R. M. Bolman, B.M., B.S., Chicago

Two forms of pathologic calcification, metastatic and dystrophic, occur in the myocardium. The metastatic is associated with hypercalcemia, decalcification of the bones and deposits of calcium salts in various tissues of the body. The dystrophic variety follows retrogressive changes in the myocardium, and the calcium content of the blood is unchanged. Previous damage, usually toxic, initiates the dystrophic deposition of calcium salts, whereas the metastatic variety is associated with a disturbance of calcium metabolism and occurs in unchanged myocardium.

Reports of dystrophic calcification extend from 1783 to the present time.[1] They record these tissue alterations as having been associated with influenza, myocarditis, nephritis with myocarditis, chronic pulmonary tuberculosis with nephritis and myocarditis, septicemia with glomerulonephritis, acute rheumatic fever, arteriosclerosis with cardiac insufficiency, fetal endocarditis,[2] chronic bronchitis with emphysema and syphilis, congenital syphilis,[3] diphtheria,[4] poisoning with corrosive sublimate,[5] lead or carbon tetrachloride, and infection with Bacillus paratyphosus.[6] All agree that deposition of calcium follows retrogressive changes in the myocardium, such as necrosis. According to Mönckeberg,[7] the condition occurs frequently in children.

Hart [3] expressed the belief that hyaline or amyloid degeneration or glycogen infiltration was the chief precursor in the myocardial damage leading to dystrophic calcification. Fatty changes not being observed in the calcified muscle fibers, he concluded fatty degeneration had no relation to the deposition of lime. Oheim [4] expressed the opinion that regressive changes of the myocardium progressed in a definite sequence, calcification being the end result. Because fatty degeneration was so marked, Nachoetschnaja [8] suggested that the focal necrosis was associated with decomposition of the fat and secondary calcification. Fatty degeneration with calcification being present in 3 of the 10 cases in which Fischer [2] made postmortem studies, he stated that a direct interrelation between fatty degeneration and calcification was indicated.

From the Henry Baird Favill Laboratory of St. Luke's Hospital.

1. Scholz, T.: Virchows Arch. f. path. Anat. **253**:551, 1924.
2. Fischer, B.: Frankfurt. Ztschr. f. Path. **3**:706, 1909.
3. Hart, C.: Frankfurt. Ztschr. f. Path. **3**:706, 1909.
4. Oheim, L.: Beitr. z. path. Anat. u. z. allg. Path. **100**:222, 1938.
5. Tilp: Verhandl. d. deutsch. path. Gesellsch. **15**:471, 1912.
6. Rüther, A.: Ztschr. f. Kreislaufforsch. **21**:313, 1929.
7. Mönckeberg, cited by Oheim.[4]
8. Nachoetschnaja, A. K.: Centralbl. f. allg. Path. u. path. Anat. **33**:276, 1923.

Fatty degeneration of the myocardium was described by Roth,[9] who drew no conclusions, and by Rüther,[6] Tilp[5] and Thorel.[10] Rüther stated the belief that focal changes in the chemical composition of the muscle caused the deposition of lime. Aschoff and Kaufmann[11] considered calcification a regressive metamorphosis of heart muscle except in the metastatic form, in which the deposits of calcium were part of a generalized metabolic defect. Schmidt[12] hypothesized an altered solubility of the blood calcium in nephritis. Erb,[11] noting an increase in the calcium salts of the blood with nephritis, explained calcification as a sequence of an unstable solution or suspension of calcium in the blood as a phosphate, carbonate or calcium-protein complex, any one of which might be precipitated by an increase in the alkalinity of the blood or by changes in the protein or carbon dioxide content or in the quantity or arrangement of the calcium salts. He mentioned hyaline degeneration as the most likely precursor of calcification. Wells[11] also hypothesized a tissue substance having a special affinity for calcium.

Little is known of the time necessary for deposition of calcium following the action of causative agents. Tilp's[5] patient died within five days after ingestion of mercury bichloride, and microscopically calcification was present. Oheim[4] reported that 6 patients had died between the third and ninth days, and 2 on the thirteenth day, after the onset of the disease. Macroscopic calcification was present in 2 patients and microscopic calcification in all. He expressed the opinion that the changes began in the myocardium between the second and the fourth day of a toxic disease and that interstitial edema and lysis of the muscle progressed until approximately the seventh day and were then followed by growth of fixed tissues, fatty degeneration, leukocytic and lymphocytic infiltration and, finally, calcification. In patients who recovered, repair of the myocardium probably began by the tenth day.

All except Oheim considered the wall of the left ventricle as the region of predilection for dystrophic myocardial calcification. Oheim considered the right ventricle, the papillary muscles or the septum as the site of predilection.

REPORT OF CASE

A white boy aged 12 years entered St. Luke's Hospital in the care of Dr. N. C. Gilbert, Aug. 11, 1938, because of weakness, abdominal distention, anemia, increased weight of three months' duration and dyspnea of two months' duration. Five months before admission he had scarlet fever. The illness at first was uncomplicated. Acute bilateral otitis media developed after several weeks. One month after the onset of scarlet fever, albumin was found in the urine and shortly thereafter blood. The patient was weak to the point of exhaustion and gained weight rapidly. He was confined to bed; his weight increased. He became more anemic, and ascites developed. He entered the hospital with marked generalized anasarca. The blood pressure was 162 mm. of mercury systolic and 126 diastolic. The heart was slightly enlarged, and there was a systolic thrill with a soft presystolic murmur at the apex. The left side of the chest was dull, breath sounds

9. Roth, M.: Cor.-Bl. f. schweiz. Ärzte **14**:226, 1884.
10. Thorel, cited by Rüther.[6]
11. Cited by Scholz.[1]
12. Schmidt, cited by Scholz[1] and Rüther.[6]

and fremitus were absent, and expansion was decreased. There were ascites and anasarca. For several months his temperature ranged between 98.6 and 100 F. The urine excreted in twenty-four hours ranged between 100 and 1,100 cc. and contained between 10 and 40 mg. of albumin per hundred cubic centimeters. The urine contained granular and waxy casts, lymphocytes and a few red blood cells. The nonprotein nitrogen of the blood ranged between 54 and 100 mg. per hundred cubic centimeters; the urea nitrogen, between 34.5 and 60 mg.; the creatinine, between 2 and 4 mg. The albumin-globulin ratio varied from 1.2 to 2 Gm., and the serum protein, from 3.84 to 4.24 Gm., per hundred cubic centimeters. The sedimentation rate was 33 mm. per hour. The alkali reserve of the blood on admission of the boy to the hospital was 31 volumes per cent. The calcium of the

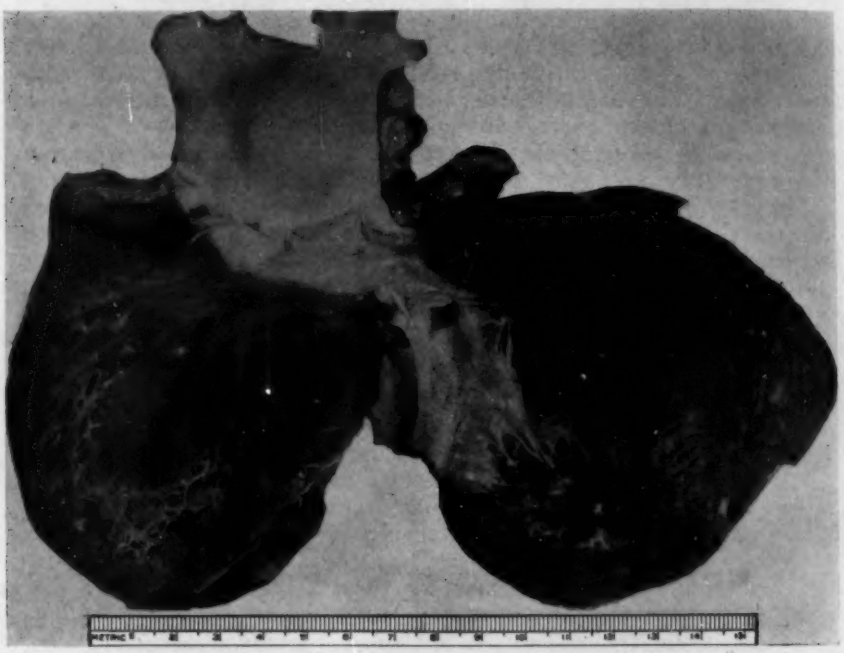

Fig. 1.—Photograph illustrating the extensive dystrophic calcification of the myocardium.

blood ranged between 7.4 and 8.2 mg. per cent. From the time of his admission the patient's condition became slowly worse, and he died March 17, 1939, seven months after entering the hospital and about one year after the onset of scarlet fever.

The essentials of the anatomic diagnosis on postmortem examination were: marked diffuse subacute glomerulonephritis with nephrosis; marked general anasarca; ascites; marked calcified fibroplastic myocarditis and fatty changes of the myocardium.

The lining of the right auricle, right auricular appendage and right ventricle was smooth. There were no unusual changes of the pulmonic, tricuspid, mitral or aortic valves of the heart. Under the endocardium of the right ventricle were small regions of fatty change. The lining of the left auricle, left auricular

appendage and left ventricle was smooth. The thickness of the myocardium of the left ventricle measured behind near the septum at the level of the mitral ring was 1.4 cm.; at the apex, it was 1 cm., and midway between, 1.2 cm. There were no changes in the root of the aorta. The orifices of the coronary arteries were widely patent. On broad surfaces made by cutting the myocardium of the left ventricle, there was a red-brown fibrillar tissue mottled with yellow and gray scars. The septal myocardium was similar. The gray-yellow regions contained calcium plaques ranging to 1 cm. in maximum dimensions. They were scattered extensively throughout the myocardium of the left ventricle (fig. 1). The lining of the coronary arteries had marked fatty changes and calcified plaques. The heart weighed 350 Gm.

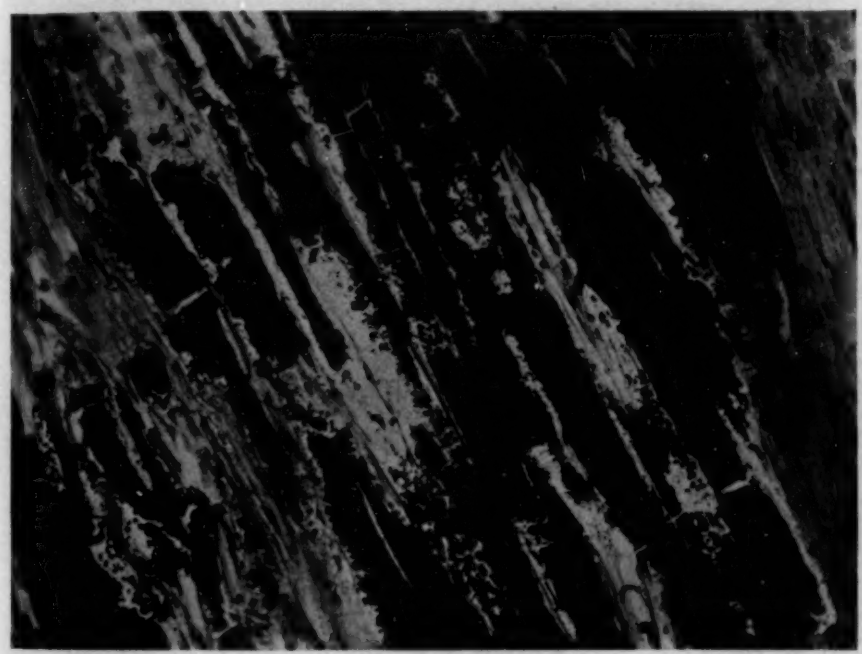

Fig. 2.—Photomicrograph illustrating the calcification of the myocardial fibers; × 198.

The routine histologic examination of the cardiac tissues substantiated the anatomic diagnosis. Large portions of the myocardium were replaced by hyaline fibrous tissue. Some myocardial cells were necrotic or in stages of retrogressive change. These cells were pale and granular, and their nuclei stained poorly. In the necrotic and fibrous tissues were large plaques of a granular basophilic debris corresponding to calcium deposits (fig. 2). These hard basophilic plaques in the myocardium were chemically calcium phosphate and calcium carbonate. Tissues fixed in formaldehyde solution, sectioned and stained with sudan III had marked fatty changes of the myocardium in the regions with calcification.

The kidneys grossly were pale; the subcapsular surfaces were granular, and histologically they had the glomerular and other changes of subacute glomerulonephritis.

Cultures of blood from the right ventricle of the heart and of the pericardial and pleural fluids were sterile.

COMMENT

The dystrophic calcification of the myocardium of this patient was associated with marked fatty changes of the cells, necrosis and scar tissue replacements. In almost all reports of this disorder mention is made of fatty degeneration as a precursor or a coincidental change. The details of the process leading to this retrogressive change in the myocardium are not known, but the change probably develops from disturbances in cellular metabolism because of the systemic disease—in this patient, nephritis.

The lipids in the myocardium are complex mixtures. Which, if any, of these is concerned with the deposition of the calcium salts can only be postulated, namely, the fatty acids. Hartsuch [13] observed that fatty acids in contact with dilute alkaline aqueous solutions of base give up hydrogen ions to the water phase in exchange for the basic ions. When the soap compound thus formed is relatively insoluble in the aqueous medium, the base accumulates in the oil phase, which gradually becomes supersaturated and the soaps precipitate. This reaction occurs freely in the p_H range of body fluids or tissues. The fatty acids in the lipid deposits, accordingly, attract the calcium salts to form compounds which undergo further molecular changes.

SUMMARY

Dystrophic calcification of the myocardium was associated with subacute glomerulonephritis in a boy aged 12 years. Marked fatty changes of the muscle tissues, necrosis and replacements with scar tissue occurred with the calcium deposits.

The dystrophic calcification is correlated with the fatty acid content of the lipids.[13] According to this view, water-insoluble calcium soap accumulates in fatty acid mediums when they are in contact with an aqueous phase containing bases at the p_H of tissue fluids. Further molecular changes in the organic calcium compounds lead to the formation of calcium carbonate and phosphate.

13. Hartsuch, P. J.: Arch. Path. **25**:17, 1938.

RHABDOMYOSARCOMA OF THE CORPUS UTERI

CHARLES M. CAMPBELL JR., M.D., BOSTON

Malignant tumors composed chiefly or in part of cells which bear a structural resemblance to striated muscle cells have been recognized for nearly three quarters of a century. Such tumors are rare but have been described arising in many different parts of the body. The most common site of origin of such tumors is along the course of the urogenital tract. The present one is a rhabdomyosarcoma of the corpus uteri, being the twenty-second arising in this site which has been reported in the literature.

REPORT OF A CASE

A 68 year old housewife entered the Peter Bent Brigham Hospital, July 27, 1938, complaining of vaginal bleeding of approximately ten months' duration. Fourteen years previously she passed uneventfully through the menopause at the age of 54, after having had three children. In October 1937 bleeding occurred, lasting for four days, with no pain. This was interpreted by the patient as a normal period. Three weeks later a similar episode occurred in which the bleeding was more profuse and bright red. In December 1937 and February 1938 she again had a flow of blood for seven and ten days, respectively. In February she began to notice discomfort low in the abdomen, accompanied by bearing-down pains. She was aware that her abdomen was becoming somewhat larger. From April 1, 1938 until her admission she noticed marked urinary frequency, nocturia with micturition four or five times nightly. During these three months she had an almost continual vaginal flow except when she was in a recumbent position. She lost approximately 5 Kg. of weight in this period. For a few weeks before entry she had a hacking cough and night sweats. Her family history was noncontributory, and her past history was uneventful.

Physical examination revealed a well developed obese elderly woman in no apparent pain or distress. The temperature was 37 C. (98.6 F.), the pulse rate 90 and the respirations 31 per minute. The height was 160 cm.; the weight, 71.2 Kg. The head, heart and lungs were essentially normal. The abdomen was obese, but through it could be felt a firm mass, slightly tender and moderately movable, which appeared to be attached to the body of the uterus and which rose to the level of the umbilicus. Rectal and pelvic examinations confirmed the observation that the mass was of uterine origin, and the fundus of the uterus could not be definitely differentiated from the mass. The cervix showed evidence of senile atrophy but was free from erosions or tumors.

Roentgen studies of the chest previous to admission showed no evidence of metastatic malignant growth or of pulmonary tuberculosis.

Laboratory studies of the blood and urine were noncontributory, showing good renal function and no anemia or leukocytosis.

July 28, 1938, panhysterectomy, bilateral salpingo-oophorectomy and appendectomy were performed under anesthesia induced with avertin with amylene hydrate and ether. At operation the uterus was seen to be symmetrically enlarged to

From the Department of Pathology, Peter Bent Brigham Hospital.

approximately the size of a uterus in the fourth month of pregnancy, while the tubes and ovaries were perfectly normal. The uterus and adnexae were removed, and incidental appendectomy was performed. The peritoneal cavity contained no free fluid, and the liver was free from evidence of metastatic lesions. The postoperative course was uneventful, and the patient was discharged on the sixteenth hospital day without subsequent treatment in the form of irradiation. She was seen eight months after operation and at that time showed no evidence of recurrence of her disease and was able to carry on her customary activities.

Fig. 1.—The gross specimen opened along the anterior wall, showing the tumor filling the uterine cavity and the degree of retraction of the uterine wall; × ½. The cervix has been removed from the specimen.

Pathologic Examination.—The specimen consisted of the complete uterus and adnexae. It weighed 1,230 Gm. It was firm and moderately regular to palpation. The serosa was smooth, and a small subserous leiomyoma measuring 2 cm. in diameter was seen on the posterior wall. The uterus was opened along the anterior wall (fig. 1), and as this was done the wall retracted widely. The anterior wall was thin, measuring less than 1 cm. Attached to the entire posterior wall from the fundus to the internal os was a pear-shaped mass, measuring 19 by 13 by 9 cm., with the apex directed toward the cervix, completely filling the uterine cavity. This mass had a slightly irregular surface, was

firm to palpation and reddish gray. On the anterior upper right surface of the tumor mass was seen a small polypoid structure, measuring 3 by 2 by 1 cm., attached by a broad base to the tumor. Figures 2 to 5 were taken from blocks through this structure. Sections through the base of the tumor at its attachment to the myometrium showed no capsule but a moderately sharp line of demarcation. Around the base there were several irregularities appearing as soft, almost white outgrowths of tissue, measuring up to 7 by 5 by 2 cm.

For microscopic examination blocks were taken through the base of the tumor, through the polypoid mass on the anterior surface and through the body of the

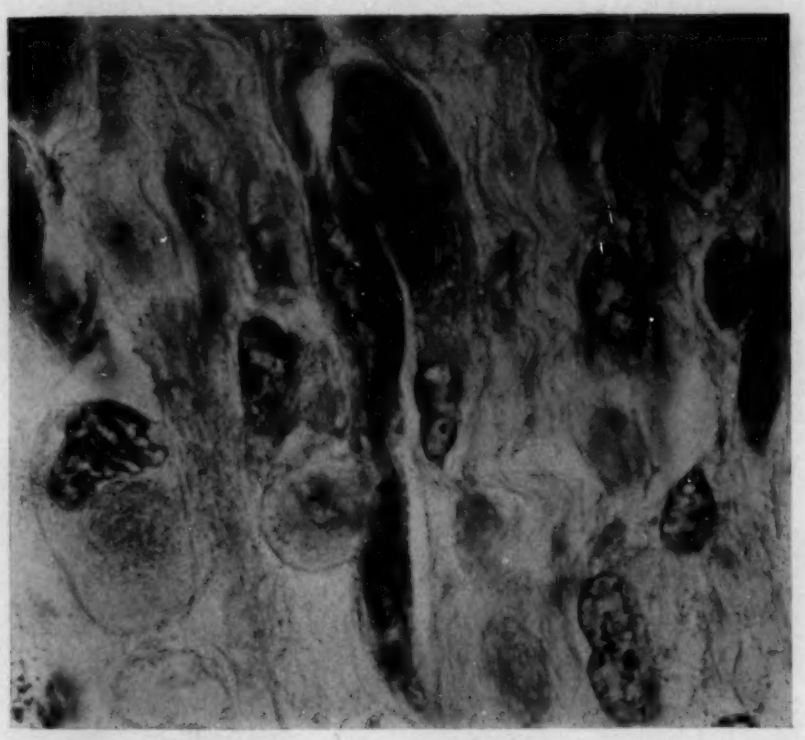

Fig. 2.—The central cell in this photomicrograph shows a high degree of differentiation. It is elongate and possesses very distinct cross striations. Mallory's phosphotungstic acid–hematoxylin; × 940.5.

tumor at random. In addition, sections were taken through the cervix, the anterior wall of the uterus and through the ovaries. The tissue was fixed in Zenker's fluid (with 5 per cent glacial acetic acid) and stained with eosin-methylene blue after embedding in paraffin. Sections which included the tumor were also stained with Mallory's phosphotungstic acid–hematoxylin, and the latter stain was found the most useful for bringing out the special characteristics of the tumor cells.

Microscopically the tumor was seen to be composed, for the most part, of rather poorly differentiated cells of variable size. The type cell possessed a pale

blue cytoplasm and an irregular nucleus in which nucleoli were seen. Numerous mitotic figures were identified in these cells. Many cells were seen scattered through the tumor which were more regular in outline and contained vacuoles of varying number and size, which resembled in all respects developing fat cells. When stained with scarlet red the vacuoles were seen to contain neutral fat. Similarly, large round eosinophilic cells were found singly and in groups, frequently with several nuclei, in which, even in the eosin–methylene blue stain, faint markings resembling cross striations could be seen. The nuclei of these cells, whether single or multiple, were often very irregular and frequently con-

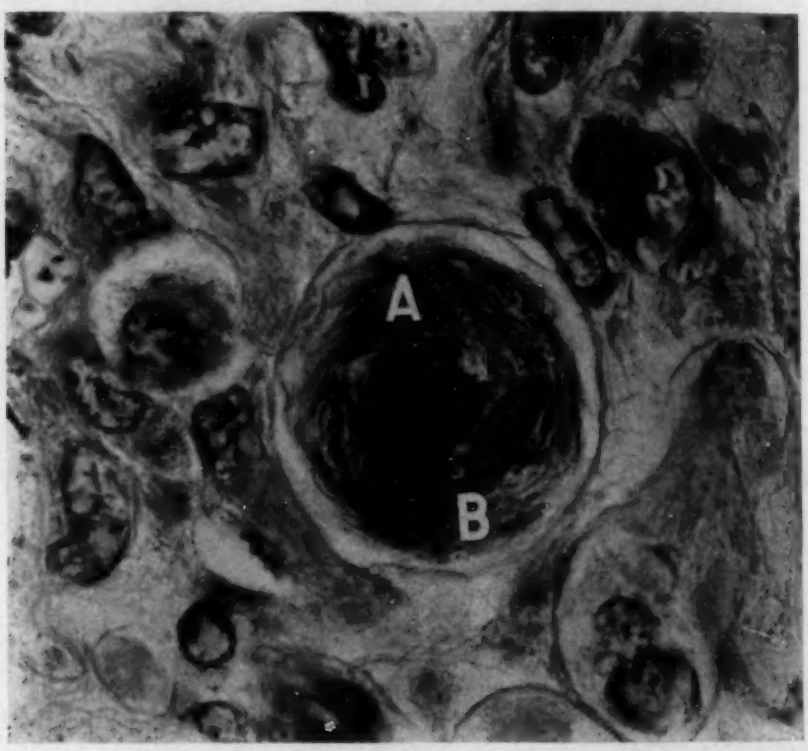

Fig. 3.—The large cell in the center shows many groups of centrioles arranged in pairs or clumps surrounded by a clear zone (*A*). Note the irregularity of the nucleus (*B*). The circular arrangement of the delicate myofibrils in the cytoplasm is typical of many cells seen. Mallory's phosphotungstic acid–hematoxylin; × 1163.

tained nucleoli. While most of the cells were round, others were extraordinarily variable as to shape, a few cells (fig. 2) showing a long spindle-like outline, representing a high degree of differentiation.

The sections through the base of the tumor showed no semblance of a capsule, yet the borderline was moderately distinct. None of the sections taken beyond the zone of grossly appreciable tumor showed any evidence of infiltration or invasion of the uterine or extrauterine tissues by tumor cells.

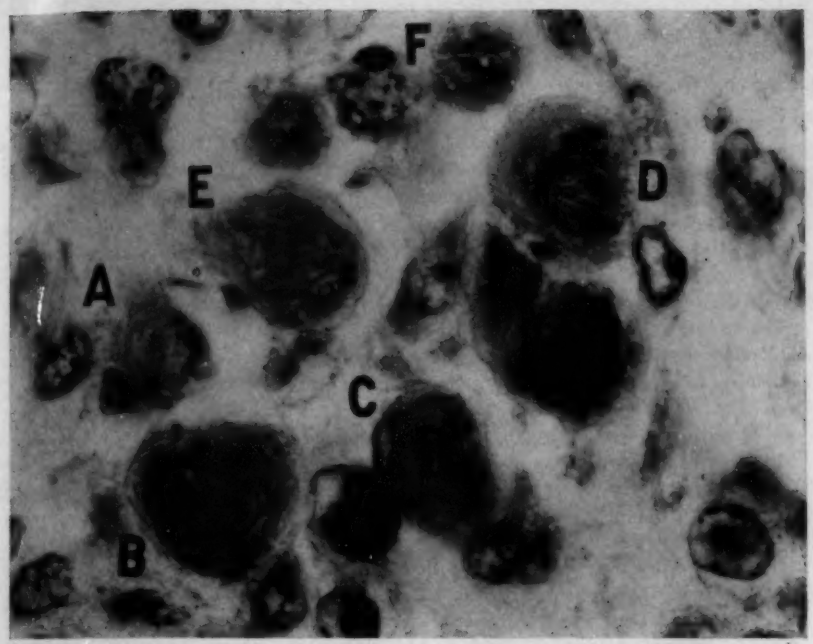

Fig. 4.—This illustrates the frequency of myoblasts in some areas of the tumor. Many cells showing varying degrees of differentiation of cross striations can be seen in this small area. The sequence (from *A* to *F*) of development from the irregularly arranged or paired centrioles to well developed cross striations is indicated. Mallory's phosphotungstic acid–hematoxylin; × 1028.

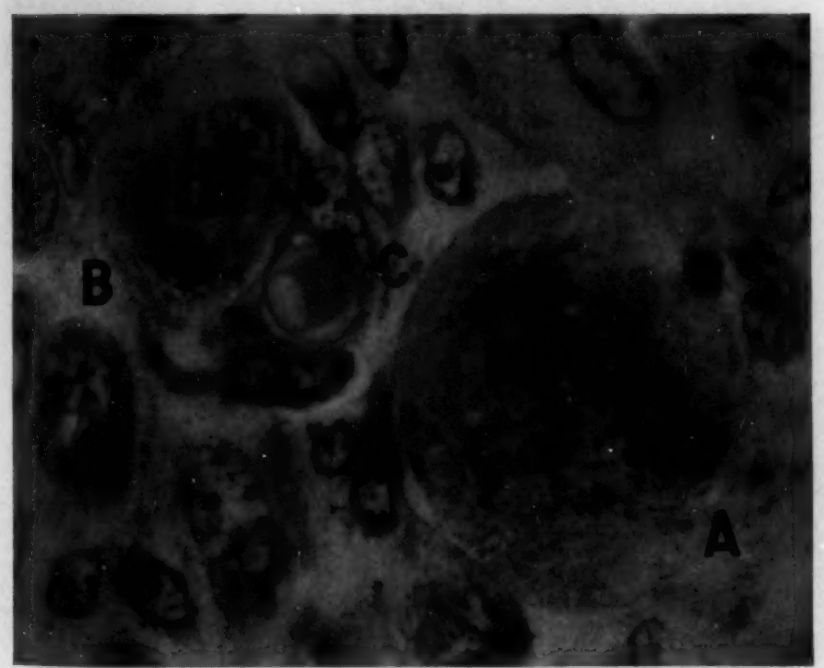

Fig. 5.—The large cell (*A*) shows the degree of variation of differentiation which may be encountered in a single cell. Note the definite cross striations and also the clumps of irregularly arranged centrioles. One other cell showing a much earlier stage of differentiation is also shown (*B*). Between these two cells lies a developing fat cell (*C*). Mallory's phosphotungstic acid–hematoxylin; × 1105.

The chief interest in the microscopic examination lay in the appearance of the large cells described when stained with Mallory's phosphotungstic acid–hematoxylin. My observations confirm the work of Wolbach in which he postulated that the myofibrils of striated muscle cells are derived from centrioles. Many authors feel that the striated fibrils develop from the mitochondria and their granules, but in the present case the evidence suggests that these structures arise from the centrioles after dispersion of the clusters of centrioles and formation of fibrils connecting the centrioles. This is probably followed by continued division of the centrioles and of the fibrils. In the present case cells were seen at all stages, from those containing irregularly arranged clumps of centrioles to elongate cells with striations morphologically indistinguishable from those seen in cells of voluntary muscle and heart muscle. These various stages are illustrated in the accompanying photomicrographs (figs. 2 to 5). The centrioles appear in the phosphotungstic acid–hematoxylin stain as dark, frequently paired small granules with a clear surrounding zone, which is occasionally biscuit shaped, and their fibrillary attachments are shown as fine, delicate, light brown material. As the later stages of development are reached, the centriolar derivatives appear as wide dark bands and their intermediary substance as light, almost clear, narrow bands (fig. 2). In the tumor there is a wide variation in the stage of development which the individual cells show. There are many myoblasts which are so early in the series that there is almost no special differentiation, while other cells show other stages of development up to the fully differentiated striated cell. This variation is noted also within single cells (fig. 5), some of which contain clumps of centrioles, easily recognizable cross striations and all intermediate stages of development of the myofibril.

COMMENT

The present rhabdomyosarcoma of the corpus uteri is of interest both from the clinical and from the pathologic standpoint. Clinically, the patient presented a condition which must be considered, despite its rarity, in the differential diagnosis of any postmenopausal bleeding, especially when a tumor mass is felt. If one excludes the 2 infants in whom rhabdomyosarcoma of the corpus uteri has occurred, this patient fell into the predominant age group and shared in the common presenting symptom of postmenopausal bleeding. The number of pregnancies of the patients whose cases have been reported ranges from 0 to 12.

Pathologically, the tumor is of interest because it shows, in the first place, a wide degree of differentiation along the various lines of mesenchymal tissue. If one assumes that Cohnheim's theory of embryonal rests is applicable to this type of tumor, one must accept the suggestion that it arises in a primitive type of mesenchymal cell which can give rise both to fat and to muscular tissue. In the cells which are obviously developing along the lines of striated muscle, all stages are seen between the primitive myoblast and the well differentiated elongate cell in which cross striations are definite and distinct. This type of tumor must be considered malignant because of the frequency of postoperative recurrence and the occurrence of local invasion as reported in the literature.

SUMMARY

A rhabdomyosarcoma of the corpus uteri is reported. The patient was a multiparous woman 68 years of age. Only 21 such tumors with this situation have been previously reported, of which 2 occurred in

infants. Panhysterectomy was performed, and no evidence of local or distant metastases was found. Follow-up studies of the patient over a period of eight months showed no evidence of progress of the disease.

Histologic study of the tumor revealed the true nature of the neoplasm and tended to support the theories of a centriolar origin of the cross striations of skeletal muscle, first advanced in 1928 by Wolbach.

REPORTS OF CASES

The literature contains reports of cases by the following authors (an asterisk indicates that the report is in a journal not available to me):

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Laboratory Methods and Technical Notes

A RAPID METHOD OF STAINING GRAM-POSITIVE ORGANISMS IN FROZEN SECTIONS

ARAM A. KRAJIAN, LOS ANGELES

The identification of gram-positive organisms, such as Actinomyces, Pneumococcus, Streptococcus, Staphylococcus, Clostridium welchii and others, is of prime importance in making a diagnosis on autopsy or surgical material in certain cases.

The Gram-Weigert method (by which staining of gram-positive organisms only is obtained) and its modifications are applicable only to paraffin sections, preferably those of tissues fixed in Zenker's fluid.

The delay and cost involved in the fixation and preparation of such paraffin sections are sufficient to make desirable a shorter and more economical method.

I have recently developed a rapid method applicable to formaldehyde-fixed frozen sections. The preparation of the sections, including cutting, staining and mounting, requires less than ten minutes.

METHOD

1. Fix tissues in a 10 per cent solution of formaldehyde for twenty-four hours or longer.
2. Cut thin frozen sections.
3. Transfer the section to a glass slide.
4. Drain and dehydrate immediately with absolute alcohol or anhydrous isopropanol. Blow on the section until all the alcohol is evaporated.
5. Blot dry.
6. Dip twice in thin celloidin (a pyroxylin preparation) blow on the section and dip in water.
7. Stain with Stirling's gentian violet for two minutes.
8. Rinse in water and apply Gram's iodine solution for two minutes.
9. Blot completely dry.
10. Flood the section with eosinol (with medicine dropper) and agitate the slide. Generally one or two applications are sufficient to remove the gentian violet and at the same time counterstain the section red. (See description of eosinol.)
11. Treat with carbolxylene for thirty seconds.
12. Treat with two changes of pure xylene, fifteen seconds each.
13. Mount in gum damnar.

Results: Gram-positive organisms (bacteria and fungi) are stained violet; gram-negative organisms are unstained; the background is bright red.

For emergency examination, fresh tissues are fixed as follows:

A 10 per cent formaldehyde solution is brought to a boil, and thin blocks of the tissue are dropped into it. The container is placed in a paraffin oven at 56 to 60

C. for fifteen minutes' fixation. Then frozen sections are prepared and stained as already described.

PREPARATION OF EOSINOL

Dissolve 5 Gm. of aqueous eosin in 10 cc. of distilled water. Precipitate it by adding 10 cc. of glacial acetic acid and 2 cc. of concentrated hydrochloric acid, and mix with a glass rod.

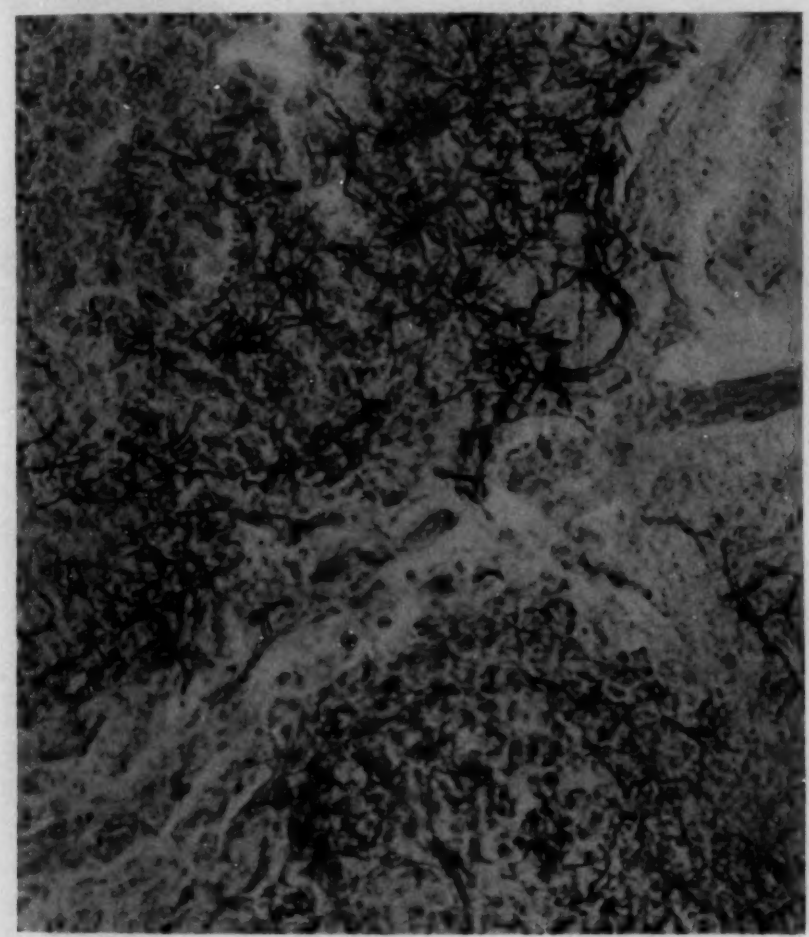

Fig. 1—Actinomycosis giving rise to widespread granulomatous lesions of the lungs; × 420. Note mycelia stained by the modified Gram-Weigert method.

Incubate the resulting coagulum at 56 C. for from twelve or sixteen hours, or until all the water has evaporated.

Dissolve this dehydrated acid eosin in 10 cc. of absolute alcohol or anhydrous isopropanol and 20 cc. of acetone, stirring with a glass rod for several minutes

and placing in a paraffin oven for two hours. Let the undissolved portion, which is to be discarded, settle to the bottom of the container. Remove the clear portion with a clean, dry pipet, add it to 1,500 cc. of carbolxylene (1 part of pure phenol crystals in 3 parts of neutral xylene). Some precipitate will form, which will settle to the bottom of the container. The clear portion is eosinol. The solution keeps indefinitely.

Fib. 2.—Torulosis of leptomeninges and cerebral cortex; × 165. Note organisms in perivascular tissue, stained by the modified Gram-Weigert method.

Owing to the variation in the staining power of various brands of powdered eosin, it may be necessary to standardize the solution by staining control sections and adjusting the strength of the eosinol by reducing or increasing the amount of carbolxylene.

Notes and News

Announcement of the Journal of the National Cancer Institute.—The National Cancer Institute of the National Institute of Health, United States Public Health Service, announces the forthcoming issue of the *Journal of the National Cancer Institute,* the official organ of the institute.

The new journal, which will be issued bimonthly, will be of the scientific type of periodical and will contain articles by the members of the staff on the various lines of cancer research work carried on by the institute.

The first issue will contain papers on the Federal cancer control program, the approaches to cancer research, the effect of various hydrocarbons in producing tumors in mice and studies on normal and cancerous tissues.

Copies of the journal will be sold to applicants by the Superintendent of Documents, Government Printing Office, Washington, D. C., who will also handle all annual paid subscriptions. The price of a subscription will be $3.00 a year in the United States.

The journal will be distributed free to a limited number of medical schools, to workers in the field of cancer research, to research institutes interested in cancer, to a limited number of surgeons, as well as to certain government depositories, and to journals making suitable exchanges.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Microbiology and Parasitology

Virus of Lymphopathia Venerea [Venereal Lymphogranuloma]. G. O. Gey and F. B. Bang, Bull. Johns Hopkins Hosp. **65**:393, 1939.

The virus of venereal lymphogranuloma has been grown and maintained in continuous roller tube cultures of a pure strain of human fibroblasts for more than seven months. The cell-free tissue culture fluid at first produced almost 100 per cent mortality in mice but later lost this power. The neutralizing power of human serum from patients who gave positive Frei reactions was demonstrated on virulent tissue culture fluid. Tissue culture fluid from specifically infected tissue cultures serves as a good antigen for Frei tests. Specific cytopathologic changes were observed and studied in living cells infected with the virus of venereal lymphogranuloma. Sulfanilamide in low concentration in the culture medium was observed to alter the course of the specific cell reaction to the presence of the virus.

From Authors' Summary.

Effect of Sulfanilamide on Experimental Tuberculosis. R. H. Follis Jr. and A. R. Rich, Bull. Johns Hopkins Hosp. **65**:466, 1939.

The present study of the effect of sulfanilamide on experimental tuberculosis in the rabbit confirms the result of a previous study on the guinea pig, demonstrating that adequate doses of the drug properly administered have a definite inhibitory effect on the development of the disease. Individual rabbits exhibit marked differences in the degree to which they acetylate the drug and in their ability to attain and maintain a high concentration of the drug in the blood following the administration of a given dosage. These differences undoubtedly play a role in determining the degree to which a given dosage of the drug will exert a beneficial effect on the progress of the infection in different animals. It is stressed that no conclusions regarding the effect of the drug on human tuberculosis should be drawn from these experiments. That is a problem that requires a separate and carefully controlled study.

From Authors' Summary.

Spirochetes and Filtrable Viruses in Frozen State. T. B. Turner and W. L. Fleming, J. Exper. Med. **70**:629, 1939.

Observations are reported on the virulence of various types of spirochetes and filtrable viruses after storage at −78 C. for periods up to three years. Five specimens of Spirochaeta pallida, belonging to four different strains, and 7 specimens of Spirochaeta pertenuis, belonging to five different strains, were tested after storage for approximately three years. All but 1 specimen contained actively motile spirochetes, and all specimens were highly pathogenic for rabbits. Many other specimens of these spirochetes stored for shorter periods were also tested, with similar results. Spirochetes of relapsing fever tested after storage for from six months to one year showed active motility and were virulent for mice. Leptospira icterohaemorrhagiae was found to be actively motile after storage for five, six and ten months. The spirochete of rat bite fever, Spirillum minus, was virulent for mice after storage for one year. The virus of human influenza, PR8 strain, tested after storage for approximately three years, was fatal to mice in

essentially the same dilution as was the same lot of material before freezing. Similar results were obtained on testing the virus of meningopneumonitis after storage for three years. The virus of lymphogranuloma venereum was pathogenic for mice after storage for ten months.

FROM AUTHORS' SUMMARY.

SURVIVAL OF SPIROCHETES IN FROZEN STATE. T. B. TURNER and N. L. BRAYTON, J. Exper. Med. **70**:639, 1939.

Titration experiments made with the spirochetes of relapsing fever before and after freezing showed the following: With each freezing and thawing there was a slight but regular decrease in virulence, a decrease which bore no relation to the duration of storage at —78 C. Ordinarily, infectivity was destroyed by more than four refreezings. There was not always close correlation between motility and infectivity. Cooling spirochetes from 0 to —78 C. over a two to six hour period damaged them only slightly more than did rapid cooling, but warming from —78 to 0 C. over a two to six hour period killed most of the organisms. Rapid thawing, as in a water bath, damaged the spirochetes less than thawing more slowly, as at room temperature. At storage temperatures of —12 and 20 C. there was a gradual decrease in virulence over a period of days or weeks, and by the sixth week the infectivity of the material was markedly reduced.

FROM AUTHORS' SUMMARY.

SELECTIVE ACTION OF SULFANILAMIDE IN EXPERIMENTAL MALARIA. L. T. COGGESHALL, J. Exper. Med. **71**:13, 1940.

It was found that with mixed malarial infections in the same experimental animal sulfanilamide eradicates a virulent Plasmodium knowlsi infection, leaving the animal with a milder, chronic Plasmodium inui infection. Determinations of the metabolic activity of the two parasites in vitro showed that P. knowlsi consumes approximately six times more oxygen than P. inui. The addition of sulfanilamide in concentrations less than that necessary to effect a cure almost completely inhibited the respiration of P. knowlsi in vitro, while the same concentrations of the drug against the same number of P. inui had no apparent effect.

FROM AUTHOR'S SUMMARY.

CARDIAC LESIONS RESEMBLING ASCHOFF BODIES IN RABBITS. L. LOEWE and S. E. LENKE, J. Exper. Med. **71**:89, 1940.

Cardiac lesions, resembling those of human rheumatic fever, have been observed in rabbits during the course of a seemingly spontaneous epizootic.

FROM AUTHORS' SUMMARY.

AVIAN TUBERCLE BACILLI IN DIPHTHEROID CULTURES. J. MCCARTER and E. G. HASTINGS, J. Infect. Dis. **64**:297, 1939.

From bovine and porcine tissues cultures of several species of diphtheroids have been isolated which when inoculated into experimental animals produced avian tuberculosis. Purified cultures of the diphtheroids did not produce tuberculosis.

Avian tubercle bacilli and these diphtheroids will grow commensally, and the growth of the tubercle bacilli may not be macroscopically detectable.

Because diphtheroid and acid-fast organisms are found in the same culture, the assumption cannot be made that the culture is pure and that the diphtheroid is one phase in the life cycle of the acid-fast organism.

FROM AUTHORS' SUMMARY.

BRAIN LESIONS IN RODENTS WITH TYPHUS AND ROCKY MOUNTAIN SPOTTED FEVER. R. D. LILLIE, R. E. DYER and N. H. TOPPING, Pub. Health Rep. **54**:2137, 1939.

Characteristic typhus nodes and vascular lesions are produced in the brain in endemic typhus fever in the old-field mouse (Peromyscus polionotus polionotus), the white-footed mouse (P. leucopus noveboracensis), the desert mouse (P. eremicus eremicus), the deer mouse (P. maniculatus gambelii), Reithrodontomys sp., gray and white mice (Mus musculus), and the white rat (Rattus norvegicus albinus). No lesions were seen in inoculated cotton mice (Peromyscus gossypinus gossypinus). The lesions in these rodents are comparable to those seen in guinea pigs but vary in the proportion of lesions of different types and in the distribution from species to species.

In Rocky Mountain spotted fever similar lesions are irregularly and inconstantly but rather frequently produced in white mice, and scanty reactions are seen in meadow mice (Microtus pennsylvanicus pennsylvanicus) and in an occasional cotton mouse (Peromyscus gossypinus gossypinus).

The increase in relative frequency of lesions of the midbrain and hindbrain in guinea pigs with spotted fever as compared with those with typhus is duplicated in white mice. The greatest number of lesions of the brain in endemic typhus in white mice are seen fourteen to sixteen days after inoculation, which corresponds closely to the time of maximum cerebral reaction in guinea pigs.

FROM AUTHORS' SUMMARY.

SUCCESSFUL TRANSFER OF THE LANSING STRAIN OF POLIOMYELITIS VIRUS FROM THE COTTON RAT TO THE WHITE MOUSE. CHARLES ARMSTRONG, Pub. Health Rep. **54**:2301, 1939.

The Lansing strain of poliomyelitis virus after adaptation to the eastern cotton rat was successfully transmitted through twelve generations of white mice.

FROM AUTHOR'S SUMMARY.

PATHOLOGY OF POLIOMYELITIS EXPERIMENTALLY INDUCED IN THE EASTERN COTTON RAT, SIGMODON HISPIDUS HISPIDUS. R. D. LILLIE and C. ARMSTRONG, Pub. Health Rep. **55**:115, 1939.

The virus of human poliomyelitis produces in the cotton rat, Sigmodon hispidus hispidus, a poliomyeloencephalitis which is closely similar in topographic distribution as well as in individual types of lesions to that observed in man and Macacus rhesus with this virus. In the brain the medulla and pons show the greatest reaction, and the cerebellar roof nuclei and midbrain the next greatest. Necrosis of nerve cells, polymorphonuclear infiltration and invasion of necrotic cells, neuronophagia, focal and diffuse cellular gliosis, vascular endothelial swelling and proliferation and lymphocyte infiltration of nerve sheaths are all observed. Other organs show no important changes.

FROM AUTHORS' SUMMARY.

BACTERIUM ENTERITIDIS INFECTIONS IN INFANTS. K. J. GUTHRIE and G. L. MONTGOMERY, J. Path. & Bact. **49**:393, 1939.

This paper describes a series of cases of infection of infants with Bacterium enteritidis (Gaertner's bacillus) and a single case of septicemic infection with Bact. enteritidis var. dublin. The majority of the cases of Bact. enteritidis infection occurred as a small epidemic in the nursery of a maternity hospital. The source of this epidemic was untraced, but the organisms were most probably milk borne. More than half of the children died. All showed moderately severe purulent catarrhal enteritis with septicemia; of those whose infection was fatal,

meningitis was present in over one third and purulent cholecystitis in one seventh. Infection with Bact. enteritidis is uncommon in young children. The present series appears to be the largest on record, and the high mortality rate with the remarkable parenteral lesions illustrates the extraordinary invasive power which these organisms assume in susceptible subjects. Meningitis has been reported occasionally in children infected with Bact. enteritidis, but the triad of enteritis, meningitis and cholecystitis recorded here appears to be unique.

FROM AUTHORS' SUMMARY.

MORGAN'S BACILLUS. A. SEVIN and R. BUTTIAUX, J. Path. & Bact. **49**:457, 1939.

Morgan's bacillus 1 differs from the other types described in possessing distinctive characters which are fairly constant in different strains and are not altered by long maintenance in artificial mediums. It fails to ferment lactose and mannitol and ferments dextrose, fructose and usually galactose with very slight production of gas. Cultures develop as a film on the surface on 1 per cent agar but not on 3 per cent agar. This character is also seen with certain O forms of Proteus but not with other intestinal organisms. Strains of Morgan's bacillus show a community of antigens, most marked in cultures on soft agar; such cultures show also serologic relationships with certain strains of Proteus vulgaris and Proteus X 19. It is considered that Morgan's bacillus 1 is to be regarded as a distinct organism related to Bacillus proteus and included in the subspecies which does not ferment mannitol.

FROM AUTHORS' SUMMARY.

SUSCEPTIBILITY OF SMALL LABORATORY ANIMALS TO SYPHILIS AND TO RABBIT SYPHILIS (PALLIDOIDOSIS). A. BESSEMANS and A. DE MOOR, Ann. Inst. Pasteur **63**:569, 1939.

Among rabbits with naturally occurring rabbit syphilis, those with testicular lesions harbored virulent spirochetes in the inguinal, axillary, popliteal and retrocecal lymph nodes for two hundred and fifty-three to five hundred and fifty days. Guinea pigs, white rats, white mice, common hamsters, golden hamsters and hedgehogs inoculated subcutaneously in the genital region acquired latent inapparent infections and harbored virulent organisms for five to one hundred and eighteen days in the inguinal and occasionally in the axillary lymph nodes. In a golden hamster and in a hedgehog the blood was infectious after eighteen and one hundred and eighteen days, respectively.

In experimental infections with Spirochaeta pallida in which the organism was inoculated into rabbits, guinea pigs, white mice, domestic mice, white rats, Norwegian rats, common hamsters, golden hamsters and hedgehogs, it was found ten to five hundred and seventy-six days after inoculation in the lymph nodes, usually in the spleen and occasionally in other organs. Invasion of the brain occurred in rabbits, white rats, white mice and golden hamsters, and virulent organisms were usually demonstrable after fifty-two to three hundred and fifty days by inoculation of rabbits. Spirochetes were usually seen in dark field examination of the brains of white mice and golden hamsters. The infections remained latent, without clinical signs or pathologic changes, except in rabbits and in a single guinea pig, the blood of which was infectious twenty-three days after inoculation. Susceptibility of the common doormouse, muscardine, squirrel and ground squirrel could not be demonstrated.

In the golden hamster the virulence of S. pallida was apparently increased, and the results suggested that multiplication occurred in the lymphatic system. This animal seems suitable for studies of syphilis.

J. B. GUNNISON.

Immunology

ANTIGEN OF LYMPHOCYTIC CHORIOMENINGITIS. J. E. SMADEL, J. J. WALL and R. D. BAIRD, J. Exper. Med. **71**:43, 1940.

The soluble antigen of lymphocytic choriomeningitis, which is readily separable from the virus, is a relatively stable substance and appears to be of a protein nature. A specific precipitin reaction can be demonstrated when immune serum is added to solutions of the antigen which have been freed of certain serologically inactive substances. The complement fixation and precipitation reactions which occur in the presence of immune serum and noninfectious extracts of splenic tissue obtained from guinea pigs dying with lymphocytic choriomeningitis seem to be manifestations of union of the same soluble antigen and its antibody. On the other hand, the antibodies for the soluble substances and neutralizing substances appear to be different entities.

FROM AUTHORS' SUMMARY.

HYDROLYSIS OF HYALURONIC ACID BY BACTERIAL ENZYMES. K. MEYER and others, J. Exper. Med. **71**:137, 1940.

An improved method is described for preparing the enzyme which hydrolyzes the polysaccharide acid contained in vitreous humor, umbilical cord, synovial fluid and the mucoid phase of group A hemolytic streptococci. Preparations have been obtained from pneumococci, group A hemolytic streptococci, Clostridium welchii and from splenic tissue which display the same specific activity. Evidence is presented to show that the hydrolytic enzyme is not the same as that responsible for the lysis of pneumococci. In pneumococci and hemolytic streptococci the major portion of the enzyme is bound to the cell structure. The enzyme from Clostridium welchii is associated with other carbohydrate-splitting enzymes in the culture medium and not with the bacterial cells. It is suggested that the disappearance of the mucoid capsule of group A hemolytic streptococci is due to enzymatic hydrolysis of the acid polysaccharide. The relation between enzyme activity and the virulence and invasiveness of group A hemolytic streptococci is briefly considered.

FROM AUTHORS' SUMMARY.

THE VALUE OF THE COMPLEMENT FIXATION TEST IN THE DIAGNOSIS OF PSITTACOSIS. K. F. MEYER and B. EDDIE, J. Infect. Dis. **64**:225, 1939.

Complement fixation tests with coctoantigens prepared from virulent mouse spleens or preferably Rivers-Li tissue cultures of the virus of psittacosis are invaluable aids in early and late diagnosis of the disease in man. Convalescent serum may shorten the course of the disease and should be tried. Highly potent goat serum may be equally effective and may be secured from the George Williams Hooper Foundation, of the University of California.

STAPHYLOCOCCUS ENTEROTOXIN. E. DAVISON and G. M. DACK, J. Infect. Dis. **64**:302, 1939.

Staphylococcus enterotoxin is relatively heat stable, but prolonged boiling or autoclaving gradually decreases its potency. It is not extracted from filtrates by chloroform. The varying results indicate that some undetermined factor controls alcoholic precipitation. However, the enterotoxin retains its potency after treatment with alcohol, while the lethal staphylococcus toxin is destroyed. It is salted out of solutions saturated with ammonium sulfate but not from those half saturated.

FROM AUTHORS' CONCLUSIONS.

A Virus-Inactivating Agent from Human Nasal Secretions. F. M. Burnet, D. Lush and A. V. Jackson, Brit. J. Exper. Path. **20**:377, 1939.

Burnet, Lush and Jackson describe an agent found in human nasal secretion which is capable of inactivating the virus of influenza and certain other viruses. Experiments with several viruses are detailed. No correlation is found between lysozyme activity and this agent. The properties of the agent are discussed, and its action is contrasted with that of desoxycholate.

Immunity to Influenza. C. L. Oakley and G. H. Warrack, J. Path. & Bact. **50**:37, 1940.

Mice that have been inoculated intranasally with living virus or vaccinated intraperitoneally with two doses of living or formaldehydized virus show development of both antibody for and immunity to influenza of varying quality and degree. The rise in antibody is fastest in the animals given two doses of living virus intraperitoneally; all three groups reach the same maximum two weeks after the first inoculation. In some mice infected intranasally antibody has disappeared by the end of six weeks; in others it may remain more than three months. Antibody persists about eight weeks in animals vaccinated with two doses of formaldehydized virus and twelve weeks in those vaccinated with living virus. Mice vaccinated with one dose of living virus intraperitoneally show poor antibody response. In mice vaccinated intraperitoneally with formaldehydized virus antibody titer and degree of immunity to the main strains run parallel. Animals infected intranasally, though in respect to antibody they show no striking difference from those vaccinated with formaldehydized virus, are immune to all four strains. After intranasal inoculation with strain W. S., its neurotropic variant, the Talmey and the Gatenby strains, the production of lesions is essential for the development of antibody and immunity. Circulating antibody can account for all the characters of the immunity to the homologous strain possessed by animals vaccinated intraperitoneally with living virus. From Authors' Summary.

Ability of Bacillus Subtilis to Produce Positive Wassermann Reactions in Serums. M. Aminoff, Acta path. et microbiol. Scandinav. **16**:376, 1939.

Serums that were negative in Wassermann tests were inoculated with 80 strains of gram-positive, spore-forming aerobic bacilli and incubated for forty-eight hours at 37 C. A majority of the 24 strains of of Bacillus cereus and of the 11 strains of Bacillus mycoides changed the serums so that they gave positive Wassermann reactions, while the majority of the 15 strains of Bacillus vulgatus and of the 11 strains of Bacillus mesentericus left the serums unchanged. The results of inoculations with Bacillus subtilis, Bacillus megatherium, Bacillus terminosporus and Bacillus centrosporus were not conclusive, owing to their small number.

I. Davidsohn.

Tumors

Cardiac Metastasis from Malignant Melanoma. V. Moragues, Am. Heart J. **18**:579, 1939.

Four cases of cardiac metastasis from malignant melanoma are reported. A review of the literature discloses only 23 such cases. Doubtless others have been reported, but under the heading of carcinoma or sarcoma. Moragues believes that cardiac metastasis of malignant melanoma is more frequent than the paucity of reported cases would lead one to think. One of the patients in whom cardiac metastasis from malignant melanoma was observed by him was a Negress. This is the first time such an occurrence in the Negro race has been reported. In none of the cases presented here was the involvement of the heart suspected clinically.

From Author's Summary.

LEUKEMIA IN THE F STRAIN OF MICE. A. KIRSCHBAUM and L. C. STRONG, Am. J. Cancer **37**:400, 1939.

Observations were made on spontaneous leukemia and lymphosarcoma in 17 mice of the F strain. Leukemia developed in 295 F mice as the result of inoculation of leukemic cells. Mice of this strain were 100 per cent susceptible to inoculation of leukemic cells. Lymphosarcoma, myelogenous leukemia and lymphatic leukemia may be grouped together as "leukemic conditions" appearing frequently in the F strain. Myelogenous leukemia was transplanted with the same technic as lymphatic leukemia, i. e., by either subcutaneous or intraperitoneal inoculation of cells.

FROM AUTHORS' SUMMARY.

HORMONES AND MAMMARY ADENOCARCINOMA IN THE MOUSE. A. LACASSAGNE, Am. J. Cancer **37**:414, 1939.

This review of numerous experimental observations brought forth in recent years by physiologists and oncologists shows the rapid evolution of the problem of the role of the hormones in the production of mammary carcinoma. Despite these advances, the factor causing cancer remains uncertain. The present state ot the problem may be summarized as follows: (*a*) Carcinoma can occur only in a mammary gland which has undergone a certain degree of development. (*b*) The development of the mammary gland is dependent on the estrogenic and pituitary hormones. (*c*) But whether these stimulating factors play a direct role in the cancerization process or only produce an anatomic development of the mammary gland sufficient to allow the cancer process to manifest itself is still undetermined. (*d*) It is of interest to compare this evolution of knowledge relative to one of the factors indispensable to the production of cancer (the hormone) to work carried on at the same time by geneticists, such as Murray, Little and Bittner, on the second indispensable factor, namely, "hereditary predisposition."

FROM AUTHOR'S CONCLUSIONS.

MAMMARY GLANDS OF MICE OF VARYING TUMOR SUSCEPTIBILITY. W. U. GARDNER, L. C. STRONG and G. M. SMITH, Am. J. Cancer **37**:510, 1939.

The mammary glands of adult female mice of strains varying in their susceptibility to mammary tumors differ structurally in that localized nodules of mammary tissue (hyperplastic, resting or regressing) occurred more frequently in the mice of the high tumor strains and were found infrequently in the low tumor strains. The number of nodules tended to increase with age but was not related to the postlactation interval or to the stage of the estrous cycle. The degree of involution of the glands could not be associated with the stage of the estrous cycle or with the age of the animals, but tended to increase with the length of the postlactation interval. Localized hyperplastic nodules occurring in mammary tissue are discussed briefly from the standpoint of their relation to possible malignant changes.

FROM AUTHORS' SUMMARY.

SIGNIFICANCE OF THE REACTION TO IRRADIATION IN CARCINOMA OF THE UTERINE CERVIX. S. WARREN, J. V. MEIGS, A. O. SEVERANCE and H. L. JAFFE, Surg., Gynec. & Obst. **69**:645, 1939.

On the basis of observations on 70 patients treated for carcinoma of the cervix the writers conclude that the histologic grade is of less importance in prognosis than the clinical classification; that the response to irradiation of either the tumor cells or the stroma is a definite guide to radioresistance, since practically all of the patients whose tumors fail to show radiation changes at early biopsy die of the carcinoma in spite of intensive radiation therapy and, further, that absence of such reaction at biopsy indicates a strong probability of the ultimate death of the patient from the cancer. In their opinion patients without radiation changes at early biopsy should be treated surgically.

WARREN C. HUNTER.

STATISTICAL REVIEW OF PATHOLOGICALLY VERIFIED AND GRADED EPIDERMOID CARCINOMA OF THE SKIN. S. WARREN and S. O. HOERR, Surg., Gynec. & Obst. **69**:726, 1939.

Five hundred and seven consecutive cases of epidermoid carcinoma observed in the twenty-five year period ending with the year 1936 are subjected to statistical review. In 75 per cent of these the malignancy was grade I; in 22 per cent, grade II and in the remaining 3 per cent, grade III. The patients numbered 486. There was a known mortality of 19 per cent. The size of the lesion when first treated is shown to influence prognosis more than any other factor; lesions larger than 5 cm. carried a mortality of 82 per cent, as contrasted with 7 per cent for those 1 cm. or smaller. Next in importance is histologic malignancy, grades II and III carrying a 5 to 20 per cent greater mortality than the less malignant grades for any given size larger than 1 cm. Other factors affecting prognosis adversely are the type of treatment given prior to hospitalization, especially treatment with radium or roentgen ray, and the presence of metastases at the time of admission. The duration of the lesion and its location in an unexposed site are of importance only so far as the size is affected. An analysis of the therapeutic results indicates that radium (used only as radon and largely as surface radiation) is less satisfactory than surgical excision. In recent years radium therapy has been increasingly restricted to the more superficial lesions. Too few patients with pathologically verified epidermoid carcinoma of the skin treated by roentgen ray are included in the series to warrant comparison. An analysis of prognoses by succeeding intervals of time shows an improvement in outlook in the most recent period (1928-1932, inclusive), explained in large part by the greater proportion of small lesions in these years rather than by fundamental improvements in therapeutic technic, thus suggesting that the best prospect for the control of cancer of the skin, as with cancer of other tissues, lies in early recognition and adequate treatment while the lesion is still small.

FROM AUTHORS' SUMMARY (WARREN C. HUNTER).

MALIGNANT DISEASES IN THE BANTU OF JOHANNESBURG AND THE WITWATERSRAND GOLD MINES. C. BERMAN, South African J. M. Sc. **1**:12, 1935.

Far from being unknown, malignant disease is fairly frequently encountered, among the extensive Bantu population in Johannesburg, South Africa, and in the Witwatersrand Gold Mines. Next to the incidence of malignant disease in the population of Ceylon (9.9 per hundred thousand) that among the Bantu (18.8 per hundred thousand) appears to be the lowest in the world. Carcinoma is much commoner than sarcoma among them. Among the Bantu of the Witwatersrand Gold Mines primary carcinoma of the liver accounted for 90.5 per cent of the incidence of carcinoma; carcinoma of the stomach is unknown; carcinoma of the skin is absent; carcinoma of the lungs is rare; carcinoma of the urinary bladder is not uncommon. The Portuguese East African Bantu appear to be six times more susceptible to malignant disease than the South African Bantu. In the Bantu urban population of Johannesburg primary carcinoma of the liver was found almost exclusively in young men (among whom it accounted for 31.9 per cent of the incidence of carcinoma in all organs); carcinoma of the stomach is relatively common among the males, especially after middle age; in the females, carcinoma of the genital system accounted for almost 75 per cent of the incidence of carcinoma in all organs. Sarcoma affects the soft structures as commonly as the osseous system. Retroperitoneal sarcoma is relatively frequent. Melanotic sarcoma is relatively rare among the Bantu.

FROM AUTHOR'S CONCLUSIONS.

Technical

FIXING AND STAINING METHODS FOR LEAD AND COPPER IN TISSUES. F. B. MALLORY and F. PARKER JR., Am. J. Path. **15**:517, 1939.

In pyroxylin (celloidin) sections of tissues that had been fixed in alcohol and treated with a mixture of a fresh alcoholic solution of hematoxylin and potassium phosphate, lead stained blue. Methylene blue gave a more intense blue effect. The latter stain could also be used on tissues that had been fixed in Zenker's fluid. Copper was stained deeply blue with the same stains in alcohol-fixed and in formaldehyde-fixed tissues. The method is recommended for the study of cirrhotic livers and of the nervous system in cases in which lead poisoning is suspected. It is advisable to fix tissues in solution of formaldehyde U. S. P., in alcohol and in Zenker's fixative.

I. DAVIDSOHN.

APPARATUS FOR FREEZING AND DRYING VIRUS. J. H. BAUER and E. G. PICKELS, J. Exper. Med. **71**:83, 1940.

The apparatus described was designed for the desiccation under uniform conditions of large quantities of yellow fever virus in the frozen state. Several hundred cubic centimeters of virus material, distributed in small containers, has been desiccated simultaneously to almost complete dryness and with no appreciable loss of infectivity. Good preservation of the virus activity is insured by sealing the containers either while evacuated or after filling with dry nitrogen.

FROM AUTHORS' SUMMARY.

DESICCATION OF FILTERABLE TUMORS AND OTHER BIOLOGIC MATERIALS. R. KNOX, J. Path. & Bact. **49**:467, 1939.

Desiccation is a valuable method of preserving labile biologic substances. To obtain the best results the method used must insure that the material dried suffers little or no loss of activity either during the early stages of the process or during the subsequent storage. In the early stages it is desirable that the material should be maintained in the frozen state, and experimental evidence suggests that the rapidity and degree of freezing affect the biologic activity of the dried product. No less important are the conditions of storage; material which is not kept in properly sealed containers deteriorates rapidly. The materials so far dried by the method described include immune serums, complement and the filtrable fowl tumors. With immune serums and complement the experience of other workers has been confirmed—that desiccates show no loss of titer when compared with fresh material. With the filtrable fowl tumors highly active desiccates have been obtained. Even in high dilution these produce tumors in approximately the same time as do fresh tumor extracts of equivalent strength. The dried product is easily powdered, and when cell debris has been removed by light centrifugation it gives a uniform suspension suitable for experimental work. Filtration of dried material through a Berkefeld N candle has been successful and Berkefeld N filtrates of fresh material have been successfully dried, though with some loss of activity.

FROM AUTHOR'S SUMMARY.

Society Transactions

NEW ENGLAND PATHOLOGICAL SOCIETY

SIDNEY FARBER, *President*

BENJAMIN CASTLEMAN, *Secretary*

Regular Monthly Meeting, Jan. 18, 1940

Central Nervous System Changes in Vitamin Deficiency States. S. BURT WOLBACH.

The material presented represents chiefly the work of Drs. Roy L. Swank and Otto A. Bessey.

The underlying purpose of this work as a departmental endeavor was to learn something about myelin—whether it should be regarded as an intracellular or an extracellular material, and how it is maintained, or what light could be thrown on this by studies of degeneration and repair. As a control, some careful studies were made of wallerian degeneration following nerve sections and also studies of nerves in rats maintained for long periods in low nutritional states. Careful studies of the nervous system in vatimin B_1 deficiency and in vitamin A deficiency have been completed.

With a long-continued inadequate dietary regimen there is marked depletion of myelin in the peripheral nerves, and there is fairly prompt restoration following adequate nutrition. During the period of myelin degeneration the Marchi technic shows marked blackening. This can be readily distinguished from true degeneration. The studies of vitamin B_1 deficiency are grouped under three headings: (1) vitamin B_1 deficiency with a low caloric intake; (2) complete vitamin B_1 deficiency with an adequate diet; (3) inadequate intake of vitamin B_1 with an adequate diet. In group 2, opisthotonos occurs in about seven to twelve days, with practically no true nerve degeneration. In group 1 there are rapid loss of weight and weakness of the legs in thirteen to thirty-four days, often followed by opisthotonos a few days later. Study of the peripheral nerves shows very marked effects of starvation with some true degeneration. In group 3 weakness of the legs and paralysis develop. Opisthotonos does not occur. Other evidences of vitamin B_1 deficiency occur, such as hydropericardium, bradycardia and edema of the lungs and muscles. The peripheral nerves show extensive degeneration.

Some quantitative relationships were presented in regard to carbohydrate intake and thiamine requirements. The opisthotonos resulting from acute deficiency is to be regarded as a consequence of interference with the function of the cerebrum and essentially a physiologic decerebration. The consequence of the chronic deficiency is a lower neuron phenomenon. Degeneration in the peripheral nerves begins at the periphery and works toward the center. The longest nerves are affected first. In the severest deficiencies the ganglion cells undergo degeneration.

The studies of vitamin A deficiency have probably clarified the controversial situation that has existed. The studies show that it is possible to have marked effects of vitamin A deficiency in many organs, as illustrated by keratinizing metaplasia, without lesions of the nervous system other than depletion effects such as are constant in the control animals maintained on an inadequate caloric intake. Degeneration of peripheral nerves and certain tracts in the spinal cord may be produced with regularity in young rats, if precaution is taken to prevent storage of vitamin A before the rats are placed on the completely deficient diet. In our experience, rats which have reached the age of 10 to 14 weeks without neurologic

manifestations will not exhibit degeneration of nerves no matter how long the deficient state is maintained. We have come to the conclusion that in order to produce nerve lesions in consequence of vitamin A deficiency, there must be absolute deficiency at an early period before myelination of the nervous system is completed. In this connection it is to be recalled that at birth there is no demonstrable myelin in the rat. In contrast, the guinea pig, which is born with an almost completely myelinated nervous system, does not exhibit paralysis, although further, more rigid experimentation is required before we can be categoric on this point. Before we can conclude that vitamin A is essential for the full development of certain neurons, we must exclude the possibility of consequences of pressure on nerves due to skeletal changes. This work is still in progress.

The important conclusion in regard to the studies of the vitamin A–deficient animals is that the atrophy and metaplasia of epithelial tissues are unrelated to nerve lesions.

COMMENT

STANLEY COBB (by invitation): I think that all who have worked with the Marchi technic realize that Dr. Wolbach has made a real advance. In retrospect I realize that in the past I overlooked a lot of starvation effects, considering them artefacts. The finding of the starvation effect, on one hand, and real wallerian degeneration, on the other, explains it all very well. In the use of the word "wallerian" I wonder if we are extremely accurate—if we should use it to designate these conditions with vitamin deficiency. I think it was originally used in connection with nerves actually sectioned and was applied to an effect of injury to the nerve. The use of it raised in my mind one question that I should like to ask. Dr. Wolbach stated that he always had earlier and more degeneration at the distal end, but from the photographs it looks as if he had a withering from the end of the axon inward. I wonder if he would also have it in control nerve sections without vitamin deficiency.

S. BURT WOLBACH: We did not study the effects of sectioning the nerve in the same way that we studied degeneration, but Dr. Bessey may have more first hand information. After the nerve has been sectioned, the myelin goes simultaneously throughout the whole of the distal part. I think that the order Swank found in vitamin B_1 deficiency indicates a very intimate relationship between the maintenance of myelin and the axis-cylinder. I use the term "maintenance" with the conviction that myelin is a labile substance and undergoes reversible changes promptly, relatively simple changes, involving a simple type of chemistry, but there is probably some activity going on all the time.

STANLEY COBB: I was surprised at the extremely rapid development of the lesions, some appearing after only a number of hours. I worked on larger animals (dogs), but the changes occurred after a much longer period. I wonder if there is any relation between the rate of development of the lesions and the animal's metabolic rate.

S. BURT WOLBACH: The length of time for myelin sheath degeneration to develop is longer the larger the animal. It is longer in the rabbit than in the rat, longer in the dog than in the rabbit and longer in man than in the dog.

STANLEY COBB: In our dogs we had, as a rule, this reaction of opisthotonos along with convulsions after about thirty days, or even forty-five days. This work was done a number of years ago, and then we did not know how to make a diet as accurately with respect to vitamin B_1. Since these animals have rigidity and opisthotonos there must be a central lesion, a rapidly reversible one. One wonders about acute swelling, and I should like to ask if Dr. Wolbach examined the brains of these animals for swelling of the oligodendroglia. This reversible reaction has been reported in human patients with stupor and acute mental upsets. Elvidge, of Montreal, has proved that this reversible reaction occurs by making trephine holes in the skulls of patients and examining these lesions both during the acute stage and after recovery.

S. BURT WOLBACH: Regarding Dr. Cobb's experiments with dogs, I think the fact that dogs are put into opisthotonos and brought out rapidly and then exhibit nerve lesions is confirmatory of Swank's conclusions. Incidentally, any one who undertakes pathologic studies of vitamin deficiencies should collaborate with a biochemist and a good one at that. That is one lesson we have learned in our department.

OTTO A. BESSEY (by invitation): I should like to make a suggestion as to the cause of opisthotonos. Dr. Cobb spoke about swelling of the brain. As a chemist I should like to bring up the point that this might be due to a disturbance of a chemical mechanism within the cell which leads to a disturbance of function. There is some evidence for this in the quick recovery of the bird when vitamin B_1 is given. Recently we have been able to predict when this symptom will develop in birds by cocarboxylase analysis of the brain. Cocarboxylase is the compound which is made from vitamin B_1 in the body. If you bring birds into the deficiency acutely, they will go into opisthotonos when the cocarboxylase of the brain has reached a certain value. If the deficiency is produced slowly, there is time for cocarboxylase to be transferred from the muscles, so that the brain never drops below the threshold and head retractions do not occur, but peripheral degeneration develops. Breast muscle in the pigeon has an enormous store of B_1 in the form of cocarboxylase. I should like to present this as a reason for head retractions in acute deficiency and their absence in chronic deficiency. The other point is about the early changes in the nerve. I have an important point on that, although I am afraid I am stealing Dr. Wolbach's answer. It is that the osmic acid stain used in these experiments is more sensitive to early changes than the Marchi method and that may be part of the explanation of why these changes appear early.

S. BURT WOLBACH: Relative to your explanation, Dr. Bessey, and information you have in regard to the cocarboxylase range, what Dr. Cobb had in mind was a morphologic change in the oligodendroglia, which is supposed to be concerned in myelin formation and myelin maintenance, just as the Schwann cell is for peripheral nerves. It is reasonable that some changes might occur in these cells, and in regard to the swelling of these cells I should have answered by saying that we have made cursory studies of the brain with simple stains, such as cresyl violet and eosin–methylene blue, with no special emphasis on oligodendroglia.

LEO ALEXANDER: Dr. Wolbach's paper contains a number of extremely important new facts. First of all, he has described a fundamentally new type of nerve change, namely, myelin depletion without degeneration, i. e., loss of myelin without accumulation of degeneration products giving the Marchi reaction. This depletion of normal myelin is associated with a shift of the remaining normal myelin substance from the lipoid body of the myelin sheath into and about the trabeculae of the myeloaxostroma network, thereby leaving the main body of the myelin sheath depleted of normal myelin substance. This depletion effect was seen by Dr. Wolbach in starvation and in the early stages of degeneration prior to clinical and pathologic evidence of true degeneration. The important point is that this depletion or starvation effect is not associated in Dr. Wolbach's experience with any clinical disability of the animals; it may precede such disability, or in the case of starvation, clinical disability may never result at all. By this new finding Dr. Wolbach has reversed the order of the negative or incomplete correlation of clinical and pathologic observations in deficiency diseases of the peripheral nerves. While in the past investigators were puzzled by clinical phenomena without morphologic correlates, which forced them to the assumption of a biochemical lesion preceding morphologic change, they are now faced with the existence of a morphologic change preceding clinical and physiologic disability. The discovery of this subtle but definite morphologic change will no doubt give new stimulation to clinicopathologic research in the field of early vitamin B_1 deficiency.

Another important message of Dr. Wolbach's paper is the fact that vitamin B_1 is the only vitamin the deficiency of which causes true nerve degeneration, i. e., real Marchi or wallerian degeneration with accumulation of degeneration products

giving the Marchi reaction, as well as the associated clinical picture of neuritis or neuropathy. The lack of any other vitamin in the adult animal cannot cause the clinical or pathologic picture of true nerve degeneration. The fact that vitamin B_1 is the only antineuritic vitamin was known to earlier investigators, but the literature of more recent times has tended to cloud this fact, probably as a result of technical mistakes and erroneous interpretations of the Marchi picture by various observers. Dr. Wolbach has rendered an important service in clarifying this point.

The third point which Dr. Wolbach's paper brings to mind is the reemphasis of Funk's theory of the correlation of the vitamin B_1 requirement with the caloric intake. This fact is extremely important and plays a great role in clinical work. Some of our patients with chronic alcoholism, who come into the hospital somewhat starved and dehydrated but without marked polyneuritis, show a flare-up of their polyneuritis after being put on a high caloric diet. We have found that similar to the high caloric intake, vitamins other than B_1 raise the vitamin B_1 requirement.

The fourth point of importance in Dr. Wolbach's paper is the demonstration that acute complete deficiency causes predominantly central disturbances, while chronic and incomplete deficiency causes predominantly peripheral changes. This finding is confirmed by clinical observations. Many of our patients with chronic alcoholism who have been on a complete vitamin-deficient regimen may show severe encephalopathic syndromes with comparatively insignificant changes of peripheral nerves and skin, while others who have a great deal of cutaneous and peripheral nerve lesions with no or little cerebral involvement usually give a history of more prolonged but less complete vitamin deficiency.

With regard to the hyperkeratinization of vitamin A deficiency, I should like to ask Dr. Wolbach whether in experimental animals there is follicular hyperkeratosis of the skin similar to that which is seen occasionally in patients with chronic alcoholism which clears up under treatment with vitamin A.

S. Burt Wolbach: In regard to hyperkeratinization of the skin in man, I have seen nothing comparable in animals, such as the guinea pig and rat. Also, it does not occur in children. That was brought out by the studies of Frazer and Hu, who first reported it in human subjects in the Orient, particularly in China, and they stated that it occurred only after puberty. Recently I reviewed a large number of skins of guinea pigs and rats without finding any pronounced epidermal effect.

Orville T. Bailey: This study of Dr. Wolbach's emphasizes the fact that the myelin sheath has a very active metabolism. Studies of many types indicate that it changes a good deal in varying conditions. This was brought out particularly in the studies of Speidel, who made direct observations of the nerves in tadpoles' tails; he showed that tadpoles subjected to starvation showed a marked degree of myelin change, which was reversible. Dr. Wolbach approached this problem from a different angle, that of vitamin deficiencies. These studies indicate the complexity of the chemical arrangements in the myelin sheath and suggest that various chemical compounds which have been isolated do not tell the story entirely. Some of the most recent studies on the tobacco mosaic virus by roentgen ray diffraction have indicated that forces tend to hold chemical groups together over greater distances than was previously supposed possible. Some such forces may be operating in the myelin sheath.

S. Burt Wolbach: In answer to the question of how deficiencies operate, may not some of the consequences of deficiencies be due to atrophy of ductless glands? There is no question whatsoever that it is an entirely logical approach, because if an animal with vitamin A deficiency is brought to the point of death through the deficiency one finds marked atrophy, particularly of the thyroid gland. The thymus atrophies, but I do not know what function the thymus has. So far as I have been able to see the pituitary does not atrophy to any striking degree in any deficiency.

BUFFALO PATHOLOGICAL SOCIETY

ERNEST WITEBSKY, *President*

SAMUEL SANES, *Secretary*

Feb. 10, 1940

Endometrial Sarcoma. WALTER L. SYDORIAK and NORMAN W. ELTON.

In 1,075 hysterectomies at the Millard Fillmore Hospital since Jan. 1, 1930 primary endometrial sarcoma was encountered twice. The women were both in their sixties and at least ten years past the menopause. The chief symptoms were pain and vaginal discharge of from three days' to seven months' duration. In only 1 case was the tumor palpable, although both patients had appreciable uterine enlargement. In each specimen the transition from normal endometrium to tumor was clearly demonstrable. In 1 instance the sarcoma was associated with leiomyoma. Histologically, the sarcoma associated with leiomyoma was of the deciduoid type; in the other instance the sarcoma was of the undifferentiated round cell type. Neither had any striated muscle fibers such as were found in the rhabdomyosarcoma of the endometrium recently diagnosed by Bohrod and reported by Gunning and Ross. In addition, endometrial sarcoma has been noted in association with carcinoma of the corpus uteri in 2 of 55 specimens of the latter type of carcinoma. In both patients the carcinomatous element of these compound tumors metastasized.

Glycolysis in the Spinal Fluid of Patients with Meningitis. ROGER S. HUBBARD and ERWIN NETER.

An extension of the studies on the glycolytic enzymes of cerebrospinal fluid in epidemic meningitis previously reported (*J. Clin. Investigation* **15**:519, 1936) is presented. Observations on specimens from a third patient which were incubated at 38 C. for twenty-four to forty-eight hours confirmed the findings previously described. Early in the disease, when the concentration of polymorphonuclear leukocytes in the fluid was high, this procedure resulted in a decrease in the concentration of the dextrose but not in that of the fructose. The change was noted in fluids from which micro-organisms were not isolated on routine culture. After the cell count had fallen to 150 per cubic millimeter, no reduction in dextrose was obtained. Incubation of a fluid containing polymorphonuclear leukocytes and pneumococci (type XVII) resulted in complete disappearance of both dextrose and fructose. When a fluid from a patient with tuberculous meningitis containing 500 lymphocytes per cubic millimeter was incubated, the concentration of neither sugar was significantly altered. Incubation of dextrose with a heavy suspension of leukocytes isolated from the blood of a patient with leukemia produced destruction of the sugar, but in a control incubation of the cells with physiologic solution of sodium chloride a substance giving the fructose (resorcinol) reaction was extracted, and therefore such a suspension did not seem suitable for a further study of the differential glycolysis of the two sugars.

When spinal fluids from patients suffering from various clinical conditions not pyogenic meningitis were heavily inoculated with meningococci and incubated at 37 C., significant destruction of dextrose was not demonstrated in any instance. These experiments could not be considered completely satisfactory, for in most of the more nearly normal specimens of fluid the organisms were not viable after twenty-four hours, and although viability was sometimes demonstrated after longer periods (forty-eight hours) in some specimens (notably in specimens from 2 patients recovering from anterior poliomyelitis, containing about 0.2 per cent protein and a moderately increased cell count) significant multiplication of the organisms was not obtained at any time.

Incubation of very heavy (grossly cloudy) suspensions of meningococci in physiologic solution of sodium chloride extracted very small amounts of a compound giving the fructose (resorcinol) reaction. These experiments are in accord with the thesis previously presented and recently discussed by Hendry (*Arch. Dis. Childhood* **14**:307, 1939) that a destruction of the dextrose in spinal fluid is brought about by incubation with polymorphonuclear leukocytes. They probably do not prove that the meningococci do not play at least a part in the glycolysis produced on incubation of fluid from patients with epidemic meningitis, for the multiplication of micro-organisms obtained in the control experiments was not as great as that frequently noted in fluids from patients suffering from this disease. The extraction of small amounts of a compound giving the resorcinol reaction for fructose from heavy suspensions of leukocytes and of meningococci on incubation with physiologic solution of sodium chloride shows that this factor must be taken into account when the concentration of fructose in body fluids is studied.

Shigella Sonnei in an Infection of the Urinary Tract. E. WITEBSKY, R. CARTER and C. RICHBART.

There are a few reports in the literature concerning dysentery bacilli of the Shiga and Flexner groups in urinary infections. These organisms not infrequently appear either in pure culture or in mixture with other organisms causing infections of the urinary tract. Most of the patients were females. The binding of dysentery bacilli in infections of the urinary tract is significant mainly from the standpoint of epidemiology. From a study of the literature it seems to be rare to find Shigella sonnei in urinary infections. A case in Brazil was reported by Pacheco.

Our patient complained of pains in the region of the left kidney and of hematuria for two weeks. The intravenous urogram showed normal kidneys and ureters and a stone in the lower third of the left ureter. While in the hospital he had daily a temperature of 102-103 F. Anorexia, nausea and vomiting occurred for one week; then a small stone was passed. Following this, the patient recovered. During his stay in the hospital he was treated with sulfanilamide.

As far as the previous history is concerned, the patient mentioned a severe attack of diarrhea with bloody stools and fever, occurring eleven years ago.

Bacteriologic examination of the urine of the patient revealed two nonlactose-fermenting organisms: one, a member of the genus Alcaligenes; the other one, Shigella sonnei. The biochemical reactions of the latter strain were typical for Shigella sonnei. The strain, suspended in saline solution, was agglutinated up to the end titer when kept in the water bath at 55 C. The serum of the patient did not contain any agglutinins against this strain. The second culture, taken after the stone had passed, did not reveal the presence of any gram-negative bacilli.

CHICAGO PATHOLOGICAL SOCIETY

S. A. LEVINSON, *President*

EDWIN F. HIRSCH, *Secretary*

Regular Monthly Meeting, Feb. 12, 1940

Histologic Changes in Tumors Implanted with Radon Seeds. PERRY J. MELNICK.

As a continuation of studies begun five years ago, transplantable rat tumors were implanted with radon seeds. The results confirmed previous observations on similar tumors treated with roentgen rays. Two effects are clearly demonstrated. Massive doses destroy tumor cells by radiation necrosis. When the

dose is protracted or divided, a second effect becomes prominent, which consists of an interference with the mechanism of cell division, so that giant tumor cells are formed. These abnormal cells retrogress with calcium deposits appearing in their nuclei. At the lower intensities no changes in the blood vessels and other normal structures were found. Even in regions receiving 12 to 15 threshold erythema doses for two weeks arteries, veins, lymphatics, nerves and other structures remained intact. Above this dosage, however, damage to normal structures occurred, especially with the higher dose intensities. Mesenchymal reactions and fibrous induration occurred only after the tumor cells had degenerated. Fibrous induration occurred in normal structures only when these tissues were injured by high intensity or large doses. No growth of connective tissue occurred with the lower intensities. Thus, with divided or protracted treatments in the therapeutic range, no sealing of lymphatics or fibrous tissue growth was noted. With divided or protracted doses, normal tissues recover, but the nuclei of the dividing tumor cells accumulate mutation-like radiation changes.

This method of study correlated the changes in the tissues with the dosage and the time of exposure. In general, in the Flexner-Jobling carcinoma necrosis occurred within the first two or three days when 20 or more threshold erythema doses were given. The usual radiation necrosis developed after a latent period of about five days and required from 6 to 8 threshold erythema doses. Mutation-like pleomorphism ending in complete degeneration through the changes described developed in fourteen to sixteen days and required an average of 3.8 threshold erythema doses.

DISCUSSION

F. W. HARTMAN: Both fractional and massive doses of roentgen rays produce necrosis of the kidney. The effects on the renal tissues are nonspecific, although some tissues are more susceptible than others. I do not think that tumors can be destroyed and other tissues spared, such as muscle or adrenal.

VICTOR LEVINE: Dr. Melnick's report of this study was well received at the Third International Cancer Congress. The discussion emphasized that he had demonstrated clearly the greater efficacy of fractional over massive doses. In practice, fractional daily doses of 100 r with variations in port locations are given until each port has received 2,000 r. With such methods of treatment I have observed the same results in human as in experimental tumors, i. e., a selective necrosis of the tumor but not of the basic tissues.

P. A. DELANEY: Does the intranuclear deposit of calcium cast a shadow in the roentgen film?

PERRY J. MELNICK: The term "fractional radiation" is ambiguous, since the amounts used in different laboratories are not uniform. With the fractional doses that I have used there was no injury to the normal tissues. Near the location of the radon seed there is an injury, but this is caused by the intensity of dosage. There are also collagenous tissue changes secondary to the destruction of the tumor tissues. The nuclear calcification is microscopic and does not appear in roentgen films.

Histologic Study of the Distribution of Vitamin A in the Human Body under Normal and under Pathologic Conditions. HANS POPPER.

In frozen sections of tissues fixed for a short time in solution of formaldehyde U. S. P. a striking green fluorescence of certain lipoids was observed, which faded during observation under the fluorescence microscope. The same fading of fluorescence was seen with concentrates of vitamin A. The distribution of this fluorescence in the body agrees with the distribution of vitamin A as demonstrated by chemical analysis. The fluorescent inclusions have the same histologic reactions as vitamin A. Animal experiments yield the best evidence that this characteristic fluorescence is due to the presence of vitamin A. Whereas in normal rats different organs have the characteristic fluorescence, this reaction is absent in vitamin A–

deficient rats. If deficient rats are fed with vitamin A the fluorescence is visible again and agrees with the amount fed and demonstrated chemically, as, for example, in the liver. The examination of the spontaneous fluorescence can be extended by staining the lipoid carrier substances with fluorescent dyes and alternating the observation in direct and in polarized light.

In the human liver vitamin A is found in five places, namely, in the Kupffer cells, in fat droplets, in small acetone-soluble droplets not demonstrable by the usual fat stains, in lipofuscin and diffusely in the cytoplasm. There is less of the characteristic fluorescence in malnutrition. In local fatty changes there is much vitamin A in the droplets, whereas in fatty livers the fluorescence of the fat is slightly reduced. In local hepatic damage, as in passive hyperemia or infarct, the vitamin A content is locally reduced. In diffuse damage, as in cirrhosis or in acute atrophy, only traces are found, sometimes with severe fatty changes. The glomerular and fascicular layers of the adrenal in the adult are rich in vitamin A. In exhausting diseases this vitamin is either focally or diffusely reduced. The adrenal of the newborn has no vitamin A fluorescence. In the testicle of the adult the fluorescence is visible in the cells of Leydig, superimposed over a brown pigment, and in the tubular cells. It is absent in old age. In the ovary of the mature woman vitamin A is found in the subcapsular layer, in the granulosa cells and in the theca lutein cells. Small amounts of vitamin A are seen in the fat cells; the smaller the fat droplets the stronger the fluorescence. The normal kidney does not reveal vitamin A, whereas in nephritis with a nephrotic component the vitamin was found in the tubule cells and in the interstitium.

The epithelium, except for special examples, was found free of vitamin A. As here the first signs of the avitaminosis appear, a distant effect is to be assumed. Vitamin A seems to be related to fat metabolism. Its presence permits a differentiation of physiologic fatty changes from pathologic ones, in which it is absent. The histologic examination for vitamin A is simpler and in some respects better than the chemical analysis.

The Demonstration of Vitamin A in Hypernephroid Carcinoma of the Kidney. ALEX B. RAGINS and HANS POPPER.

A relation between vitamin A and tumor growth is assumed. The vitamin A content of tumors was studied by means of fluorescence microscopy because this technic makes possible a reliable estimation of the fluorescent content in the tumor cells. One hundred and thirty-nine tumors were studied. Thirty-eight contained vitamin A in various amounts. The vitamin was usually found in tumors arising from organs which normally are rich in it.

Hypernephroid carcinoma (10 cases) was particularly rich in vitamin A, whereas the normal renal parenchyma did not contain this vitamin. The distribution of vitamin A in the hypernephroid carcinoma often was parallel with the distribution of vitamin A in the glomerular and fascicular layer of the adrenal gland. Vitamin A also was found in the papillary portions of hypernephromas. A cortical adenoma and a mucin-producing adenocarcinoma of the kidney had no vitamin A. The benign adenoma of the adrenal cortex is rich in vitamin A, even though the adrenal itself is poor. These results suggest an origin of the hypernephroid carcinoma from adrenal rests.

Vitamin A was seen in solid tumors of the ovary. In xanthofibromas it was in fine anisotropic droplets of the connective tissue-like cells. In granulosa cell tumors vitamin A was distributed in two types of cells. One contained it in similar fine droplets without double refraction; these cells resembled the granulosa cells of a corpus luteum. The other contained it in larger droplets with double refraction; these cells resembled the theca lutein cells. It was found in a dysgerminoma and in epithelial cyst tissues of a malignant teratoma of the ovary.

Vitamin A was found also in a lipoma, a lipoblastoma, a hepatocellular carcinoma and in carcinomas containing large cells such as those found in the breast and prostate. The presence of fat, however, does not always lead to storage of

vitamin A, since some fat-containing tumors are free of vitamin A. It is also absent in fatty degeneration of tumors.

DISCUSSION OF REPORTS BY DR. POPPER AND DRS. RAGINS AND POPPER

O. SAPHIR: This is an entirely new method, and the limitations of interpretation are not known. If the method develops into a useful procedure, it may help to distinguish hypernephroid tissues in the kidney, ovary and elsewhere. It would be helpful also in differentiating lutein tumors of the ovary.

PERRY J. MELNICK: Is there any relation of vitamin A to carcinogenic substances?

S. ROSENTHAL: Vitamin A seems not to be present in all of the lipids in a fatty tissue.

H. C. SWEANY: Was vitamin A observed in the lipids of the brain?

HANS POPPER: Lipid droplets with fluorescence are the only ones demonstrated by this method. Other substances have fluorescence but different from that believed due to vitamin A. The brain lipids are not fluorescent. In tumors the fluorescence is not due to the circulating blood; there must be a specific affinity with the lipids. There is no vitamin A in atherosclerotic lesions of the aorta. Nothing is known about the carcinogenic properties of vitamin A.

Genesis of Pericarditis: A Review and Discussion of Three Hundred Cases. BUDD C. CORBUS JR.

Galen is said to have observed pericarditis in animals and to have concluded that the disorder occurs in human beings. Since Richard Bright's classic description of this complication as observed by him in 8 of 100 patients with nephritis examined post mortem, little has been added concerning the causes of this disease, although it occurs approximately as often as subacute bacterial endocarditis. Authors at first classified pericarditis into primary and secondary. The former was a result of infections with bacteria which entered the blood stream presumably through an undiscovered focus and produced the changes in the pericardial sac. Secondary infection was believed to occur by hematogenous invasion from the pleura or from the mediastinum, by lymphogenic spread from contiguous foci, such as burrowing splenic or hepatic abscesses, or empyema or by gastrointestinal performations into the pericardial sac. A primary disease, except external trauma or tuberculous infection, is doubted by some.

The incidence of pericarditis complicating chronic nephritis varies from 4 to 14 per cent in different parts of the world. Whether it is toxic or bacterial in origin seems to be disputed. In from 40 to 50 per cent of the cases this form of pericardial lesion is sterile by culture, while in the remainder it contains pneumococci, colon bacilli or streptococci. Foreign reports state that pericarditis is encountered in approximately 6 per cent of all autopsies. The commonest associated diseases are rheumatic fever, tuberculosis, nephritis, lobar pneumonia, sepsis and neoplastic disease. Between the years of 1928 and 1935, 7,270 postmortem examinations were performed at the Cook County Hospital. From an extensive study of the autopsy records, a classification of pericarditis and a discussion of its genesis are offered, based on a series of 300 cases. The genesis of pericarditis may be simplified if the foremost pathologic process accompanying it is emphasized. The incidence of pericarditis is analyzed under the headings of pulmonary, cardiac, renal, tuberculous and miscellaneous infections. This emphasizes that the causes of pericarditis may vary just as the incidence of coexistent morbid anatomic processes may vary in different parts of the world. Pericarditis most frequently was a complication of pulmonary infection. This seems to contradict the current opinion that rheumatic heart disease is the usual cause of pericarditis. Infections of the upper part of the urinary tract and cardiac lesions were found next in the order of frequency. In 11 of the 300 cases presented pericarditis was the so-called primary condition; i. e., pericarditis

appeared foremost and unrelated to any other demonstrable process within the body. Briefly, pericarditis was observed in 4.58 per cent of 7,270 autopsies at the Cook County Hospital. Intrathoracic suppuration accounted etiologically for the largest number of cases of the secondary type.

DISCUSSION

I. DAVIDSOHN: This report emphasizes the importance of disease of the lungs as the source of pericarditis. If evidence of healed pleural lesions were included, such as fibrous adhesions between the lungs and the pericardium, the percentage would be much greater.

V. LEVINE: Pericarditis is regarded as a common complication of the exanthematous diseases. This is not my experience in children.

S. A. LEVINSON, *President*

EDWIN F. HIRSCH, *Secretary*

Regular Monthly Meeting, March 11, 1940

Real Phosphatase in Experimental Nephropathies. OPAL E. HEPLER, J. P. SIMONDS and HELEN GURLEY.

In dog and human kidneys phosphatase is distributed in a narrow zone next the lumen in the epithelium of the outer two thirds to three fourths of the proximal convoluted tubules, i. e., within the labyrinth, and is absent or scanty in the straight or distal portion that lies in the medullary rays and in the outer stripe of the outer zone of the medulla. It is not present in the epithelium of Henle's loop or in that of the distal convoluted and collecting tubules.

Pathologic calcification of the kidneys occurred in dogs within twenty-eight hours after the animals received intravenous injections of 3 mg. of mercury bichloride per hundred cubic centimeters of blood and was marked in those that survived for three to four days. It was not present after three days in kidneys showing an approximately equal degree of tubular damage induced by uranium nitrate and potassium bichromate.

With mercury bichloride nephrosis, pathologic calcification occurs chiefly along the corticomedullary junction, while phosphatase is most abundant in the outer part of the cortex. This enzyme, therefore, probably does not enter into the formation of calcium deposits in the kidney except possibly when it is present in cellular debris in the lumens of the tubules.

DISCUSSION

EDWIN F. HIRSCH: Were the deposits of calcium associated with fatty changes of the renal cells?

J. P. SIMONDS: Fatty changes in the cells were noted, but the studies of their relation to the calcium deposition have not been completed.

Changes in Carcinoma of the Uterine Cervix Induced by Radiation. J. F. SHEEHAN.

The histologic changes induced in carcinoma of the uterine cervix in 14 patients by treatment with 800 kilovolt roentgen rays were discussed and exemplified by lantern slides. The material studied was obtained by serial biopsies. The dose administered was about 1,000 r weekly for four weeks.

In general, there was a rough correlation between the total amount of radiation administered at any given stage of therapy and the histologic changes produced. This was particularly true in transitional cell carcinoma. The changes after

the application of 1,000 r consisted of moderate cytoplasmic and nuclear swelling; after 2,000 r had been given, the changes were more marked swelling of cells, beginning loss of the regularity of the tumor pattern and the appearance of large hyperchromatic nuclei. After 3,000 r increased swelling of cells, disappearance of the cytoplasmic boundaries, complete loss of regularity in the tumor pattern and an increase in the number of bizarre cells, with giant hyperchromatic nuclei or multiple nuclei, were prominent features. After 4,000 r, marked diminution in the size of the masses of tumor cells was found, with complete disappearance of much of the tumor and the conversion of most of the remaining cells into bizarre-shaped structures, principally irregular, hyperchromatic giant nuclei with or without surrounding cytoplasm. Other changes were noted, but those mentioned were the principal ones. The conversion of most of the tumor cells into bizarre-shaped structures, principally cells with giant hyperchromatic nuclei, was considered the most characteristic change produced by radiation. A complete report was published in *The Journal of the American Medical Association* (**112**:17, 1939).

DISCUSSION

W. SCHILLER: Many reports describe retrogressive changes of carcinoma cells under the influence of radiant energy. Are there any cell changes specifically characteristic of irradiation?

PERRY J. MELNICK: Carcinoma of the cervix is the favored tumor for studies of radiation therapy. The earlier studies were with massive doses; the later, with fractional. The changes in experimental tumors of animals are like those observed in carcinoma of the uterine cervix.

EDWIN F. HIRSCH: Did these marked changes of the tumor cells influence their recurrence?

M. BOHROD: The changes observed in irradiated tumors occur also in tumors never treated. Is it possible that irradiation increases the normal rate of these cell changes?

J. F. SHEEHAN: When the changes of the cells are slight, they are not specific. Alterations of the blood vessels and cells indicate radiation effect. In some of these patients carcinoma recurred within two weeks after the roentgen ray treatment. Injury to the carcinoma cells affects their offspring, which have a lowered vitality.

Inhibition of Growth and Regression of Brown-Pearce Testicular Carcinoma Associated with Coincident Intracutaneous Growth of the Same Tumor. MAX APPEL, OTTO SAPHIR and A. A. STRAUSS.

The transplantation of Brown-Pearce carcinoma into the testicle of a rabbit results in a large tumor with diffuse metastases. Only rarely does such a tumor undergo spontaneous regression. Intracutaneous transplantation of Brown-Pearce carcinoma in the rabbit results in a tumor of the skin which soon regresses, leaving the animal refractory to subsequent transplantation of this tumor, regardless of the site of transplantation. Our experiments bring forward an additional fact, namely, that when rabbits already bearing testicular Brown-Pearce carcinoma and metastases receive intracutaneous implants of homologous tumor not only do many of the resultant tumors of the skin regress but, following this regression, the preexisting and coexisting testicular tumors and their metastases also regress. The complete report is published in the *American Journal of Cancer* (**38**:55, 1940).

DISCUSSION

I. DAVIDSOHN: There seem to be endogenous carcinogenic substances which may cause the growth of spontaneous tumors. The rarity of multiple malignant growths has been explained on the basis of immunity produced by one. One tumor may remove the carcinogenic substances. If this view is applied here, one may postulate the withdrawal of carcinogenic substances by the tumor of the skin.

The behavior of tumor tissues in the eye is difficult to explain. However, the aqueous humor is immunologically entirely different from other tissues of the body.

OTTO SAPHIR: We do not know how to explain the results; they do not seem to be explainable on the basis of immunity. There is a distinct difference also with inoculations into the anterior chamber of the eye. Tumors develop in the anterior chambers of untreated animals within two weeks after inoculation, but in four to six weeks in animals with previous injections.

MAX APPEL: It is said that men in the navy rarely have carcinoma of the deep tissues, but carcinoma of the skin commonly. Some believe that carcinoma of the skin may prevent the growth of deep-seated tumors.

NEW YORK PATHOLOGICAL SOCIETY

MAURICE N. RICHTER, *President*

D. MURRAY ANGEVINE, *Secretary*

Regular Monthly Meeting, Feb. 29, 1940

Cruveilhier-Baumgarten Syndrome. AMOUR F. LIBER and CHESTER R. BROWN.

A 39 year old white man had suffered from repeated epistaxis and severe hematemesis for eleven months, during which period he was twice hospitalized in Lincoln Hospital and once in another institution. He became jaundiced. There was moderate hypochromic anemia. Death followed repeated hematemesis. The clinical diagnosis was cirrhosis of the liver or Banti's disease.

Necropsy revealed in the subperitoneal tissue about the region of the umbilicus a group of about ten veins engorged with blood and measuring between 3 and 8 mm. in diameter. They converged to form a large vein coursing in the situation of the ligamentum teres and manifestly representing a persistent umbilical vein. This vessel was of fairly uniform caliber, measuring about 2.5 cm. in circumference. It was directly continuous with the portal vein at the porta hepatis. The junction of the two veins described a broad curve, the concavity of which was directed downward and toward the left. At the apex of this loop the vessel was distinctly wider than either the umbilical or the portal vein. The portal vein and its affluents were moderately dilated. Near the middle of the umbilical vein was an area of transverse creasing of the inner surface. The folds were not high enough to be regarded as valves. The endothelium was intact, and there was no gross phlebitis or thrombosis anywhere in the umbilical or portal systems of veins. The liver was enlarged, weighing 2,270 Gm. The entire organ was markedly flattened from above downward. The right lobe was only about half the size of the left lobe. Both on the outer surface and within the organ were numerous areas of rather coarsely nodular cirrhosis, generally surrounding fairly large branches of the portal vein. The intervening tissue was of slightly increased firmness but not grossly cirrhotic. The gallbladder and bile ducts were free of gross lesions. The spleen weighed 220 Gm. and appeared congested. In the esophagus were numerous varices, one of which was ruptured. Microscopic examination of the liver showed fibrosis of portal spaces with bands of fibrosis and lymphocytic infiltrate extending out into the lobules. Bile radicles were filled with pigment. The spleen showed diffuse fibrosis and congestion. The pancreas was fibrosed.

The presence of a greatly dilated persistent umbilical vein continuous with the sinus of the portal vein, the group of periumbilical veins at the origin of the umbilical vein and the peculiar one-sided hypoplasia of the right lobe of the liver led to the diagnosis of the Cruveilhier-Baumgarten syndrome. This was first

described by Cruveilhier in 1835. Nine cases with necropsy have been reported. In all these instances the persistence of a large vein of the umbilical system, communicating widely with the portal vein and with veins of the abdominal wall, was observed. An impressive feature, which was absent from the present case, is the tremendous development of tortuous varices running vertically in the abdominal wall. There is usually some point where a murmur and fremitus are perceived and where pressure results in collapse of the varices. This feature may be the only clue to clinical diagnosis. In some cases the persistent vein is the umbilical vein alone. In other cases it is either a paraumbilical vein opening directly into the portal system or first joining the terminal segment of the umbilical vein (rest canal), which in turn joins the portal vein. The presence of a small rest canal has been demonstrated in the majority of normal human adults. It is to be expected that in cases of cirrhosis this rest canal will undergo dilatation along with all other portocaval anastomoses. However, there are a number of features which unequivocally set apart the Cruveilhier-Baumgarten syndrome. In some cases there is no cirrhosis. The majority of cases, whether there is a cirrhotic involvement or not, present either total hypoplasia of the liver or, what is more characteristic, elective hypoplasia of one lobe, usually the right. In a few cases there was evidence that the venous anomaly was congenital. Furthermore, in the enormous majority of cases of hepatic cirrhosis with development of collateral circulation the portal hypertension does not succeed in dilating the rest canal to anywhere near the size which it attains in Cruveilhier's syndrome. The fact that in over half the cases of this syndrome cirrhosis was a feature therefore suggests that the venous anomaly predisposes to but does not necessarily result in cirrhosis of the liver. There is a possible therapeutic conclusion to be drawn from the clinicopathologic studies of these cases. If the Cruveilhier syndrome can be diagnosed clinically at a time when *no cirrhosis is present*, ligation of the umbilical or paraumbilical vein might be indicated. To our knowledge, this procedure has never been attempted.

DISCUSSION

ANDREA SACCONE: I am much interested in this presentation because there is so much confusion in the classification of this condition. I am especially interested because in the Italian literature Professor Bastai reviewed some cases of this syndrome. This review is found in *Acta clinica medica Turin* (1924-1935). He came to the conclusion that in every such case there is narrowing of the suprahepatic veins, mostly congenital, and that if cirrhosis of the liver is present one is dealing with some other form of damage to the liver, not with the Cruveilhier-Baumgarten syndrome. In the Cruveilhier-Baumgarten syndrome there is only the clinical appearance of cirrhosis of the liver, i. e., enlargement of the umbilical vein, narrowing of the suprahepatic vein, ascites and melena (Gamma). In these cases the liver had the appearance of cyanotic induration, but the author did not find real cirrhosis. The case demonstrated by Dr. Liber shows cirrhosis of the liver with enlargement of the umbilical vein, and, I am sorry, but I cannot regard this case as one of the Cruveilhier-Baumgarten syndrome according to the conclusions of the Italian school.

MAURICE N. RICHTER: How is it possible to cause collapse of veins both above and below the point of pressure?

CHESTER R. BROWN: All I can suggest is that pressure on the umbilicus stops the flow in collaterals going upward and downward from this point.

MAURICE N. RICHTER: Is it necessary that the pressure should always be on the umbilicus?

CHESTER R. BROWN: According to Eppinger's picture, it seems to be.

AMOUR F. LIBER: To our great regret, we are not familiar with the work of Bastai, and consequently it is difficult to comment on it. It is extremely interesting to learn about his observations. It is evident that in the case of narrowing of the suprahepatic veins the entire syndrome might well be caused by congestion of the liver and increased pressure in the portal vein, just as in any condition which

produces portal hypertension. In the case we observed the suprehepatic veins were examined carefully, and, as I recall, they were not narrowed. They seemed to be of normal caliber. On the other hand, it is conceivable that primary atrophy of the liver—I mean primary with respect to the suprahepatic veins—might result in small size of the suprahepatic veins, because there is less blood flowing through the liver. If this were caused by derivation of blood from the portal vein into the dilated umbilical vein, less blood would get through the liver and less blood would go through the suprahepatic vein, which one would expect to find narrowed, so that if we do come across cases such as those which Bastai described we shall still be in a quandary to find which came first: the narrowing of the suprahepatic vein or the removal of blood from the portal vein. Does it not seem that if the narrowing of the suprahepatic veins were primary the liver should be abnormally large except in the case in which there existed some unusual mechanism for draining off the excess of blood from the portal vein? If there happened to be an extremely large, congenitally permeable umbilical vein, it might afford such a mechanism, so that there may be endless possible combinations of mechanisms which might be involved, and then I am afraid we might become engaged in a morass of names and classifications which possibly overlap. But if we limit ourselves to the cases in which the suprahepatic veins do not seem to be narrowed enough to account for the whole condition and in which the liver is atrophic in part or in whole, we should still have the Cruveilhier-Baumgarten syndrome as it was described previous to Bastai's work. Many observers may not have had their attention called to the suprahepatic veins, so that the Cruveilhier syndrome as redefined may be even rarer than heretofore supposed.

In regard to Dr. Richter's question about the problem concerning the collapse of the veins by pressure on one point, I think most authors who have concerned themselves with it would like to know why it happens, as it has been the object of endless discussion, and it is not clear.

Correlation Between Clinical and Experimental Findings in Cases of Invasion of the Blood Stream by Staphylococci. BARNARD KLEIGER (by invitation) and JOHN E. BLAIR (by invitation).

It has been shown experimentally that pathogenic staphylococci may be toxigenic (producing a potent hemolyzing, necrotizing and rapidly lethal toxin) or nontoxigenic (causing disease chiefly because of their ability to establish localized areas of infection). In the present report are recorded the results of an attempt to correlate these experimentally established differences with certain clinical characteristics exhibited by patients with staphylococcic infections. For this purpose the records on 35 patients who were treated for staphylococcic infection with invasion of the blood stream in the Hospital for Joint Diseases between 1932 and December 1939 were reviewed. These patients were selected from a total of 43 such patients because the strains isolated from their blood streams were available for study, making possible a direct comparison between the effects of these strains on animals and the clinical symptoms of the patients from whom the strains were isolated.

The following observations have been made: In persons under 30 years of age highly toxigenic staphylococci cause a disease that is hyperacute and rapid in its course. Characteristically the pulse rate is very high and out of proportion to the height of the temperature. Symptoms of irritation of the central nervous system and of the gastrointestinal tract predominate. There is marked increase in the number of nonsegmented cells in the circulating blood.

Persons over 30 years of age are not affected by the toxin but by the organism itself. The course is not so rapid or so acute, and the symptoms are those of foci of infection plus gradual degeneration of body processes as seen in long-standing illness. The prognosis in this group depends on the health of the patient prior to his infection and on the location of the local or metastatic foci. In this group death resulted only when predisposing illness rendered the patient more susceptible to the infection or when the staphylococci attacked some vital organ or a region

that could not be drained. Patients resistant to the effects of the toxin are still subject to the infectious activity of the organism, regardless of whether their resistance has been induced by antitoxin or is natural, as in subjects over 30 years of age.

Staphylococcic infection of the blood stream in subjects with recurrent osteomyelitis, although an infrequent complication, is of considerable significance and in this series was always fatal.

DISCUSSION

D. MURRAY ANGEVINE: I should like to ask whether any observations have been made in this study as to the virulence of these organisms in relation to their toxicity. Secondly, I should like to know whether in the patients who died of the staphylococcic infection the authors observed arthritis or endocarditis, and if so, what the incidence was. Also, were there any metastatic infections of the eyes?

CHARLES LEWIS FOX JR. (by invitation): How did you determine the amounts of toxin that were formed by the various strains isolated from patients? I should also like to know, if you studied this, whether sulfanilamide had any effect on the production of toxin—whether any less toxin was produced when the organisms were cultured in the presence of the drug.

REUBEN OTTENBERG: Have the authors any idea as to how the organisms were distributed? I gathered that in the few patients who apparently died of toxic causes the organisms proliferated in the blood stream, somewhat in the way they did in the rabbits that received injections. I presume that those were infections of soft tissues and that the organisms entered by way of the lymphatics. I am asking that as a question. In the patients with the more chronic infections were there vascular lesions, thrombophlebitis, that fed the blood stream?

JACOB WERNE: Dr. Kleiger indicated that those under 30 had a much higher mortality than those over 30. Was any attempt made to correlate clinical findings, such as the presence or absence of endocarditis, with fatal outcome? Was there any study of the severity or extensiveness of the lesions as found at autopsy? Was there any correlation between these observations and age groups?

AMOUR F. LIBER: In the patients who were infected with staphylococci with toxic properties was focal necrosis of the myocardium observed? In a recent case at the Lincoln Hospital in which staphylococcemia was present, multiple embolic abscesses occurred in many organs; the myocardium contained numerous foci of necrosis without any bacteria or emboli being found in the myocardium, and at that time the question came to mind whether this was an index of the toxic properties of the organism.

JOHN E. BLAIR: It has become apparent to us that a report from the laboratory that a staphylococcus is found on culture is not entirely adequate. It is now possible, as all may know, to differentiate rapidly between pathogenic and nonpathogenic staphylococci by means of a simple laboratory test: the coagulase test. A pathogenic staphylococcus will coagulate rabbit or human plasma very rapidly. No other pathogenic coccus of any description does. Coagulation appears within fifteen minutes to about three hours after the cocci are introduced into the plasma. With such a simple test we can determine the pathogenic potentiality of the staphylococci, using the original culture, within a quarter of an hour to three hours after we first examine that culture. About 98 per cent of strains of pathogenic staphylococci give a positive reaction in this coagulase test. Nonpathogenic strains do not. Further than that, it is possible not only to differentiate between pathogenic and nonpathogenic strains of staphylococci, but it is possible to distinguish between toxigenic and nontoxigenic strains. We use forty-eight hour carbon dioxide cultures for toxin production. We can get almost as good practical results with the twenty-four hour culture, so that within approximately twenty-four hours of the time a staphylococcus is isolated it is possible to know not only whether it is pathogenic but also whether it produces a toxin. If an inference may be drawn from these facts, in addition to what Dr. Kleiger has described, it is that it is

possible to tell within a comparatively short time whether or not an infecting organism is toxigenic and, knowing that, to decide whether or not staphylococcic antitoxin is to be used. I do not think that every staphylococcic infection is susceptible to antitoxin therapy, for the obvious reason that many strains of staphylococci do not produce any appreciable amounts of toxin. In those cases which Dr. Kleiger has described—of very acute fulminating infection in persons under the age of 30, with invasion by highly toxigenic organisms—antitoxin does seem to be indicated. The protection, of course, is only against the toxin and not against the subsequent effect of the infection itself. There is at present no satisfactory antibacterial immunization to control or prevent establishment of metastatic lesions.

BARNARD KLEIGER: In answer to the first question about virulence, my colleagues and I have tried to express it in terms of both the production of toxin and the effects of the infection itself. We tried to stress the fact that these organisms when injected into a rabbit will kill the animal even in the absence of toxin, but after a longer period of time. We did no specific virulence tests other than that.

As for arthritis, endocarditis and infections of the eye, we did find suppurative arthritis in some cases, but it was almost invariably subsequent to osteomyelitis of an adjoining bone. Acute bacterial endocarditis was found in 2 cases. In 1 case there were some small white-centered petechiae of the conjunctivas, but no other type of infection of the eye was found.

We did not test the effect of sulfanilamide on the organisms or on their ability to produce toxin.

As far as the distribution of the organisms was concerned, it was noticed that in patients over 30 years of age the infection usually started as a local invasion. In those patients over 30 years of age whose infections were fatal the organisms were not as frequently toxigenic as in those whose infections were nonfatal. Infection began in almost any part of the body but was usually a superficial one that spread and flowed over into the blood stream. In some of these patients and in some of the children who were infected by nontoxigenic strains there was thrombophlebitis of the veins draining the infected areas.

We used 30 years of age as an arbitrary limit because none of our patients over this age showed any clinical evidence of the effects of toxin. It may be that some patients past that age are not resistant to the toxin; we have not encountered any.

Concerning focal necrosis of the myocardium, areas of necrosis were occasionally noted in some of the cases. They were usually associated with the more acute infection in persons under 30 years of age. As for the older patients who showed abscess formation, some showed a more generalized parenchymal degeneration but not this focal type of necrosis.

A Study of the Changes in the Brain in Alcoholism. LEWIS D. STEVENSON (by invitation).

This study is based on the observations at 44 complete autopsies on persons dying of conditions due to alcoholism from the third medical and psychiatric divisions of Bellevue Hospital. In 22 cases the diagnosis was alcoholic encephalopathy; in 3 cases, psychosis with somatic disease; in 6 cases, alcoholic psychosis with delirium; in 2 cases, Korsakoff psychosis; in 2 cases unclassified psychosis due to alcohol, and in 8 cases acute and chronic alcoholism. In 1 case the clinical diagnosis in the medical service was acute encephalitis, but the condition turned out to be alcoholic encephalopathy.

The principal changes in the brain which were presumably due to alcoholism and avitaminosis were atrophy and loss of cells, ependymitis, perivascular edema, occasionally an increase of vascularity in the mamillary bodies, sometimes an increase of astrocytes in places and occasionally loss of myelin in the optic nerves.

Since the pathologic changes in the nervous system in chronic alcoholism demonstrated in this presentation were relatively slight as compared with the pro-

found and fatal illness of the patients, I feel that the changes usually responsible for the death and for the clinical picture cannot be demonstrated under the microscope by methods now available.

The changes in the peripheral and central nervous system in alcoholism are often reversible, and the patients recover. These cures are brought about mostly by the exhibition of large amounts of vitamins, especially B_1 and B_2 in the diet (Jolliffe, Bowman, Rosenblum and Fein). One concludes, therefore, that alcohol per se is not responsible for most of the signs and symptoms seen in the various clinical syndromes of chronic alcoholism, nor is it the cause of most of the lesions found post mortem in the nervous system. In further support of this point of view one can cite the fact that most of the lesions of chronic alcoholism can be found in birds, rats and other animals which have been fed on diets deficient in vitamins, especially B_1 and B_2 (Davison and Stone). Wernicke's disease, for example, can be produced in pigeons (Alexander, Pijoan and Myerson). Wernicke's disease has been found post mortem in persons with dietary deficiency in which alcohol was not in any way a factor (Ecker and Woltman). Wernicke first observed the disease in a nonalcoholic subject who died of sulfuric acid poisoning (*Die akute haemorrhagische Polio-Encephalitis Superior*).

Neubürger found the lesions of Wernicke's disease, including hemorrhages and proliferation of blood vessels, particularly in the mamillary bodies but also in the midbrain, in persons suffering from carcinoma of the gastrointestinal tract and who were not alcoholic.

Korsakoff's psychosis is not always due to alcohol. There is a suggestion in a paper (Bowman, Goodhart and Jolliffe) that it may be due to deficiency of vitamain B_1.

In the present study of 44 cases of various kinds of chronic alcoholism with complete autopsies little correlation was found between the clinical picture referable to the brain and the anatomic distribution of lesions. In some of our cases virtually no important lesions were observed in the brain in spite of the severe and fatal cerebral illness. The present study does not confirm the observations and conclusions of some previous authors with regard to (*a*) frequent and severe involvement of the optic nerves; (*b*) frequent and severe lesions in the medulla; (*c*) frequent changes of importance in blood vessels; (*d*) severe ependymitis or gliosis; (*e*) important lesions in the cerebellum. Nor does it demonstrate that the lesions are always or mostly marginal.

I feel that the changes demonstrated in these 44 cases are probably due to vitamin deficiency, mostly B_1 and B_2.

DISCUSSION

AMOUR F. LIBER: Dr. Stevenson mentioned the important fact that the different kinds of drinks which are popular in different countries may produce different effects. In countries such as France, where absinthe is currently consumed, convulsions are frequently seen in those who suffer from alcoholism, and there it is the general belief among physicians that convulsions are usually the result of drinking absinthe, which is known to contain a powerful convulsant drug, thujone. In this country there is a tendency to lump together under alcoholism conditions due to consumption of all kinds of alcoholic drinks. This is perhaps true of the consumers of such drinks as well as of their physicians. It would be interesting to know whether convulsions occur in persons with alcoholism who drink absinthe, which is unusual in this country, or perhaps some other special kind of drink, and also to know whether there are any special pathologic changes in the convulsive patients.

JACOB WERNE: Did the clinicians who diagnosed deficiency of B_1 and B_2 use any quantitative methods in their measurement? I ask this because of the wide diversity of lesions and the relative inconstancy of many of them. I also should like to know whether in the patients mentioned as having nitrogen retention the possibility of hypertensive encephalopathy was considered as a possible explanation for the edema and petechiae.

With regard to the low incidence of subdural hematoma, is it not probable that the fact that the patients whose cases were presented were all hospitalized would mean that trauma did not play its usually accepted role in causing this lesion? In a series of alcoholic subjects found dead under circumstances which would easily admit of the possibility of trauma the occurrence of subdural hematoma is probably higher than that reported here.

GEORGE H. HYSLOP (by invitation): There are two or three things which occur to me in connection with Dr. Stevenson's paper. The first is the common negative correlation between either an acute or a serious clinical picture and demonstrable structural changes. I should like to combine that with the remark made by the previous discusser apropos of convulsions due to absinthe. At the New York State Psychiatric Institute and Hospital several years ago work was done to show that brain tissue might be sensitized to certain substances and that the introduction of these substances into the body would produce an acute focal as well as general cerebral reaction. One finds that some patients have an idiosyncrasy toward certain alcoholic beverages. I have had a number of patients who have had grand mal seizures within an hour or so after consumption of gin, who were able to drink other forms of alcohol or spirituous liquors with different esters and ethers in them without convulsive seizures; one of these patients went into status epilepticus for twenty-four hours. That is a serious clinical disorder. That patient recovered. One does not know what the structural changes might have been if the patient had died, but there was a general reaction which produced some kind of serious metabolic disorder not sufficient to lead to death.

The evidence of vitamin deficiency in such cases as those reported by Dr. Stevenson I am not familiar with, and I should like to hear from Dr. Stevenson what the clinical manifestations were in those having a nicotinic acid deficiency as well as in those not found to have a specific vitamin deficiency.

SHELDON A. JACOBSON: I should like to hear Dr. Stevenson say a word or two about the edema which was present. Was it of any appreciable quantity? If so, was the whole brain swollen, or did the edema fluid replace the brain tissue, or was it a molecular rearrangement of solids and fluids?

LEWIS D. STEVENSON: In answer to Dr. Liber's discussion, I think that absinthe in itself is a convulsant drug irrespective of any alcoholic content which may be associated with it. I suppose that is why it was prohibited here, and now, I think, in France and Spain. I should think the alcoholic content had little to do with the convulsions, although I have no real experience with absinthe. My patients were somewhat selected. I did not consciously select them, but I try to make myself feel I drink a different kind of alcohol as compared with these patients of mine. Most of them drank "smoke," but none of them drank absinthe. The incidence of convulsions was low, and I think you will find that many patients with epilepsy have convulsions if they drink alcohol. It is probable that some cases of alcoholism with convulsions are cases of hidden epilepsy brought out by alcohol, even in fairly small amounts. That would be my interpretation.

About Dr. Werne's question, we had only a few patients with high urea nitrogen, but certainly such patients have been shown by others to have gliosis in the brain without any alcohol at all, and of course the convulsions and other things referable to the nervous system, including hemorrhages in the retina which occur in persons with alcoholism, also occur in patients who are deprived of vitamins and who are not suffering from alcoholism. I cannot say what part the high nitrogen retention plays; we had only a few such patients in the group.

About the low incidence of subdural hematoma, we remarked it because it seemed unusual. We expected that many of these patients with chronic alcoholism at Bellevue who come to autopsy would have subdural hematoma. I can only suggest that the figures as far as they go mean that the alcoholic person must also have some trauma to produce a hematoma, although perhaps in some of the cases it is spontaneous. That is a question which never has been settled. Trauma was not known to be a factor in the hematomas in these patients, certainly not while

they were in the hospital, for all those who suffer from alcoholism are subject to trauma.

In regard to Dr. Hyslop's question about gin, it may be the juniper in the gin to which the patients are allergic. On the other hand, gin is a very potent drink, and perhaps the alcoholic content alone might have something to do with convulsions. Again one might be dealing with hidden epilepsy brought out by the strong alcoholic content of the gin.

About the nicotinic acid deficiency, as far as I know, there is no way of measuring it, and it was on clinical and therapeutic grounds alone that these cases were called cases of encephalopathy due to nicotinic acid deficiency. The characteristic triad of symptoms was: some clouding of consciousness, cogwheel rigidity of the muscles, and forced grasping and sucking reflexes. That is the clinical picture on which Dr. Jolliffe made his diagnosis. Estimations of vitamin C were made in a number of these cases, but I do not know that any method for estimating B_1 and B_2 was used.

About the edema of the brain, in about half the cases the pathologist said the subarachnoid fluid was increased; he said sometimes the brain looked edematous, and that is all I can say about that. Certainly the amount was probably pathologic. We took as microscopic evidence of edema the little rings which seem to be filled with fluid around the blood vessels and in many cases around the cells in the brain. I do not know whether it is really edema or not, but that is what we have always called edema. Certainly it is a dilatation of the perivascular spaces, which are part of the subarachnoid space.

PATHOLOGICAL SOCIETY OF PHILADELPHIA

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Regular Meeting, March 14, 1940

Crystalline Concretions in the Renal Tubules Following Sulfathiazole Therapy; Widely Patent Foramen Ovale in an Aged Woman. Harold M. Horack.

Since the acceptance of sulfanilamide and its various derivatives as effective chemotherapeutic agents, reports have appeared in the literature describing undesirable and even fatal complications directly attributable to the use of these drugs. Outstanding among these reports are the references to renal complications associated with the administration of sulfapyridine. Recently sulfathiazole (2-sulfanilamidothiazole) was introduced for experimental use and was believed to have a desirable therapeutic effect and at the same time to be less toxic and less apt to cause serious complications. So far as can be determined, the case to be reported is the first in which more than transient renal complications have been observed following the administration of sulfathiazole. The case is of additional interest because the patient, aged 77 years, had a widely patent foramen ovale and exhibited only terminal evidence of heart failure. From a brief review of the literature this seems to be the greatest age at which this lesion has been reported.

The patient was admitted to the Hospital of the University of Pennsylvania, Feb. 6, 1940, with signs and symptoms of atypical pneumonia. Roentgenograms were confirmatory, and a type III pneumococcus was isolated from rusty sputum. The heart was essentially normal. Blood culture and serologic tests gave negative results. The urine contained only a slight trace of albumin. The administration of sulfathiozole was started, with an early and favorable response, but was followed in eighty hours by oliguria, microscopic hematuria and elevation in the blood urea

nitrogen. The administration of the drug was stopped and specific serum administered. There was slight improvement in renal function, but the patient died suddenly and unexpectedly on the ninth hospital day.

At autopsy the kidneys were pale and moderately large, and in the pyramids were prominent grayish yellow linear streaks of a gritty material, which converged at the apexes and extended into the calices as fragile short cords and small masses. The renal pelves and the bladder contained moderate amounts of this material. The pelves were thickened and grossly hemorrhagic. Microscopically, the tubules were dilated; those of the pyramids were obstructed by large crystalline masses, and there were multiple small areas of intratubular and extratubular hemorrhage. There was chronic inflammatory thickening of the pelves with recent hemorrhage into the subepithelial connective tissue. The crystalline material on analysis was found to be a derivative of sulfathiazole. The heart was small (280 Gm.), and the wall of the right ventricle was thickened. The chambers were not dilated, and the valves were normal. The foramen ovale was widely patent (0.8 cm.), and the rim of the foramen was thickened and partially calcified. The secondary interauricular septum was absent, and there was a defect in the fusion of the right and left leaves of the primary septum, with the formation of a V-shaped defect in the septal myocardium. This defect, representing the primary ostium, was covered with a thick fibrous septum. The wall of the pulmonary artery was slightly thickened. The lungs were small, heavy and fibrous, and the external surfaces were finely nodular, giving a "hobnail" appearance. The cut surfaces exhibited dense diffuse reticular fibrosis and striking prominence of the pulmonary arteries. Microscopically, there was severe peribronchial and perivascular fibrosis with intense congestion of the small intervening islands of alveolar tissue. There was mild evidence of atypical pneumonia, and there was hypertrophy of the walls of the pulmonary arteries. There was chronic passive congestion of the liver, and the gallbladder contained a single calcium stone. The pancreas showed early and moderately diffuse pancreatic and peripancreatic hemorrhage with foci of fat necrosis. There were large leukoplakic lesions on the cervix, and the endometrial cavity contained several large and small endometrial polyps. There was a large flat mucosal polyp in the rectum, which showed early malignant changes with invasion of the papillary stroma. The adrenals and spleen were normal.

Some Common but Infrequently Recognized Lesions of the Mouth and Pharynx. WILLIAM E. EHRICH.

A study of the mouth and pharynx should be a part of the routine postmortem examination, for there is hardly another region of the body that shows such a wealth of lesions. Almost every disease, at least under certain circumstances, affects the mouth in a more or less typical manner, and the special diseases of the mouth, such as caries, paradontosis and gingivitis, are but a part of general pathologic conditions.

Of the common but infrequently recognized lesions of the mouth and pharynx, inflammatory processes, diseases of the blood vessels and abnormal cartilage and bone formations will be described as they occur in routine autopsy material. Inflammatory reactions, i. e., granulocytic infiltration of the covering epithelium, was not observed during the first days of life, but thereafter it was seen in the tonsils and tongue in 75 to 80 per cent, and in the salivary glands in 50 per cent, of all subjects studied. It appears to be caused by the combined action of local and general factors. In the tonsils of newborn and small infants there were granulocytic infiltrations at the borderline of lymphatic tissue and the capsule. The cause of this condition is still obscure.

As to the blood vessels of the mouth and pharynx, the tonsillar arterioles as well as the lingual arteries have a rather typical form of arteriosclerosis. The arterioles of the tonsils often show hyalinosis of the elastica, sometimes with occlusion of their lumens; while the lingual arteries often show unique nodular

calcifications of their inner elastic membrane. The latter was commonly present after the fortieth year of age, while the former was commonly found after the twentieth year. The arteriolosclerosis of the tonsils is probably a result of tonsillitis, while the arteriosclerosis of the lingual arteries seems to be conditioned by the functional strain to which the human tongue is exposed. In the veins of the mouth and pharynx the most frequent change was thrombosis of the varicosities which occur at the base of the tongue in the older person. In the majority of the persons with this condition thrombosis also occurred elsewhere in the body—for example, in the femoral or the parauterine veins. This indicates that in thrombosis general factors may be as important as local ones.

In regard to the sites of abnormal cartilage and bone formation, the capsule of the tonsil and the apex of the tongue are outstanding. In the capsule of the tonsil an island of cartilage may be observed even in the newborn infant, but is most frequently found in persons past 60 years of age, occurring in 50 to 70 per cent. While the presence of cartilage in the tonsils of the newborn infant is obviously due to malformation, that in the adult arises as a rule by metaplasia; the cartilage is elastic in nature. The formation of bone is preceded by calcification of the cartilage, and it is accomplished by a mechanism comparable to that of endochondral ossification.

Cartilage in the apex of the tongue was seen in almost every third person. However, this cartilage was hyaline in nature, and though it underwent calcification in older people, it never was seen to be ossified. Since it occurred with the same frequency in all age groups, and since it was found always at the same spot, namely, 1 cm. from the tip at the lower border of the septum, it appears to be a congenital structure, possibly a residuum of the lyssa of the carnivorous animal.

Book Reviews

Shock and Related Capillary Phenomena. Virgil H. Moon, A.B., M.Sc., M.D., Professor of Pathology, Jefferson Medical College. Foreword by Walter B. Cannon, M.D. Cloth. Pp. 442, with 30 figures and 5 charts. Price $3.50. New York: Oxford University Press.

This first edition by a pathologist gives the lesions found in both experimental and clinical shock, thus contradicting the century-old conception of Hennen that autopsies often show no cause of death in shock.

The author's purpose is expressed thus: "We undertook a study of shock, not to contribute further physiologic data, but to make observations of gross and microscopic changes." The characteristic changes in both anaphylactic and histamine shock, as well as in poisonings due to mercuric chloride, arsenic, snake venom and other agents, are visceral congestion, edema and capillary hemorrhages. In subsequent chapters, these very findings are noted in burns, heat stroke, eclampsia, toxemias of pregnancy, toxic jaundice, meat poisoning, diabetic acidosis, intestinal obstruction, peritonitis, acute pancreatitis, gas gangrene, wound shock and influenza. In secondary shock, a type of hemorrhagic edematous pneumonia is of very common occurrence. There are 22 gross and microscopic illustrations of tissues, 17 of which are of the lungs. There are no sections of the liver, skin, kidneys, adrenals or pituitary. By this selection does the author wish to leave the impression that the lungs manifest the chief morphologic changes in shock?

This monograph represents the integration of much work (533 titles). The approach is from the side of the capillary endothelium, which according to the author is the weakest point in the animal organism. The first four chapters deal with the capillaries, their anatomy, physiology and pathology, the works of Krogh, Lewis and Landis being freely cited. The vascular phenomena of inflammation and the migration of leukocytes into the affected areas are in response to products released from injured cells.

The theories of shock are reviewed again. The discussion of the relationship of venous pressure to shock is confusing and sketchy. The author holds that shock is accompanied by a fall in venous blood pressure; this is unsupported by objective measurements.

A tenth of the book is devoted to traumatic toxemia. The author lends his support to the concept that products of cellular disintegration are a factor in shock by citing his experiments in which various forms of tissue extracts when introduced into the peritoneal cavity gave rise to shock in dogs. Experiments conducted on animals anesthetized with sodium phenobarbital are criticized, as this drug alone can cause shock. The evidence gained from weighing experiments on the basis of which death in shock is attributed to loss of fluid into traumatized tissues is also questioned by the author.

The accepted facts regarding shock are discussed in a chapter. Here the essential mechanism in shock is again defined as a disproportion between the circulating volume and the capillary bed. This "lost blood" in shock is said to be found in the extensive visceral areas of the lungs, liver, kidneys and intestinal villi. The two major factors in shock are: atony and dilatation of the capillaries and anoxia; one leads to the other.

The section on the various chemical changes in the blood is incomplete, and only a few of the well known alterations are mentioned. Just space is devoted to the importance of hemoconcentration. The author feels, as did Roy in the previous century, that hemoconcentration is the earliest detectable manifestation of shock, as well as the most accurate index of its severity. This concentration of the blood may be measured by cell volume, red cell counts and specific gravity. No mention of the method of determining the last is given. The data presented seem to be erroneous in a few places. For example, on page 193, two specific

gravities of blood are given as 1.065, and the corresponding red blood cell counts differ by 834,000 cells. Again, the specific gravity and the red blood cell values on page 200 do not agree with those on page 263.

Capillary congestion has been rightfully reiterated; with this in mind it is difficult to understand Dr. Moon's failure to substantiate Cannon's oft proved work that in shock the greater the difference between the capillary and the venous blood count the graver the prognosis.

The chapter on adrenal cortical insufficiency is a review. The possible connection with status lymphaticus is mentioned. Swingle's conception that lack of cortical hormone may be a cause of shock is regarded by the author as inadequate; yet later the beneficial effect of his hormone on the maintenance of capillary tone is suggested as the modus operandi.

The occurrence of edema as a feature of shock is treated at length in a special chapter. The high protein content of this fluid indicates the magnitude of the capillary damage. Unfortunately, the amount and composition of the protein are not stated.

The concluding chapter deals with the mechanics of death.

It is a little difficult to understand why a book devoted to the pathology of shock should contain so much clinical material. The insistence on the fallacy of depending on blood pressure is well taken; prevention is stressed; suppression of traumatic foci is demanded, and the adsorption of toxic products from burned and injured areas is to be prevented, as such measures eradicate those substances which cause capillary dilatation. The fallacy of using vasoconstrictor drugs is brought forward. Restoration of blood volume by transfusion is considered better than that by gum-saline solutions. The use of oxygen is urged; the author makes the amazing statement, however, that he has been unable to find an account of its use in the treatment of shock. Hemoconcentration as measured by erythrocyte counts is depicted in 3 charts. The author's stand on the use of adrenal cortical extract is equivocal.

The strength of this book lies in the approach to a conception of shock from the alterations which occur in the capillary endothelium; this brings one closer to the fundamental laws of physical chemistry which govern the transport of substances through the nonaqueous phase of protoplasm. The suggestion is offered that in the second edition an expansion of the morphology and morbid anatomy should be made, for then will the true need for an authoritative book on the pathology of shock by a pathologist be met.

JOHN SCUDDER, M.D.

Biological Symposia. Volume 1. Edited by Jaques Cattell, Editor of The American Naturalist and American Men of Science. With a Foreword by Albert F. Blakeslee, Director of the Department of Genetics, Station for Experimental Evolution of the Carnegie Institution of Washington. Cloth. Pp. 238, illustrated. Price $2.50. Lancaster, Pa.: The Jaques Cattell Press, 1940.

This book contains the papers read at three symposiums held in connection with the recent (1938) Richmond, Va., meeting of the American Association for the Advancement of Science: "The Cell Theory, Its Past, Present and Future"; "Mating Types and Their Interactions in the Ciliate Infusoria"; "Chromosome Structure." The symposium on the cell theory (Joseph Mayer, chairman), held in celebration of the one hundredth anniversary of the theory, reveals that the theory, in fact, is much older than commonly believed. An instructive account is given of the development and future of the idea. The papers in the symposiums on chromosome structure (Theophilus S. Painter, chairman) and on mating types in protozoa (H. S. Jennings, chairman) bring fresh discussions of the developments in these fields of fundamental research of immediate interest to all students of the cell.

Books Received

CONGENITAL MALFORMATIONS. A STUDY OF PARENTAL CHARACTERISTICS WITH SPECIAL REFERENCE TO THE REPRODUCTIVE PROCESS. Douglas P. Murphy, M.D., F.A.C.S., Assistant Professor of Obstetrics and Research Associate in the Gynecean Hospital Institute of Gynecologic Research, University of Pennsylvania. Cloth. Pp. 98. Price $2. Philadelphia: University of Pennsylvania Press, 1940.

DIE AKUTE MYOKARDITIS. KLINISCHE UND PATHOLOGISCH-ANATOMISCHE BEOBACHTUNGEN BEI 36 KRANKHEITSFALLEN IN IHREN BEZIEHUNGEN ZU HERD-INFEKTEN, ZU ALLGEMEIN-INFEKTEN (GRIPPE) UND ZU TUBERKULOSE. Ferdinand Wuhrmann, Oberarzt der Klinik. Paper. Pp. 148, with 86 illustrations. Basel, Switzerland: S. Karger, 1939.

EXPERIMENTAL POLIOMYELITIS. Morris Schaeffer and Ralph S. Muckenfuss, Department of Health, Bureau of Laboratories, New York. Published under the auspices of the National Foundation for Infantile Paralysis. Paper. Pp. 158. Lancaster, Pa.: The Science Press Printing Company, 1940.

CHEMICAL COMPOSITION OF FOODS. R. A. McCance and E. M. Widdowson. Medical Research Council, Special Report Series, no. 235. Cloth. Pp. 150. Price $1.20. New York: British Library of Information. London, England, His Majesty's Stationery Office, 1940.

REPORT OF THE MEDICAL RESEARCH COUNCIL FOR THE YEAR 1938-1939. Presented by the Lord President of the Council to Parliment by Command of His Majesty, January 1940. Committee of the Privy Council for Medical Research. Paper. Pp. 171. Price 90 cents. New York: British Library of Information. London, England: His Majesty's Stationery Office, 1940.